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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent 6,525,060

HARDERN et al. Atty. Ref.: 3764-205; Confirmation No. 2221

Appl. No. 09/508,195 TC/A.U. 1624; Issued: February 25, 2003

Filed: March 8, 2000 Examiner: Ford, J.M.

For: TRIAZOLO(4,5-D)PYRIMIDINE COMPOUNDS

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September 9, 2011

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

LETTER

Pursuant to its obligations under 37 C.F.R. § 1.765 and in accord with § 1.785, the patent owner confirms through its agent below that applications for extension of patent term under 35 U.S.C. § 156 based on the regulatory review period for BRILINTA™ were filed for the present patent and for U.S. Patent Nos. 6,251,910, 7,250,419 and 7,265,124. The patent owner awaits in due course an election requirement for patent term extension of only one of the four patents.

Respectfully submitted,

NIXON & VANDERHYE P.C.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION FOR EXTENSION OF PATENT TERM (37 C.F.R. § 1.740)

Pursuant to 35 U.S.C. §156(d) and 37 C.F.R. §1.740, AstraZeneca UK Limited ("Applicant") as Assignee and legal owner of the above-captioned patent, hereby petitions for extension of U.S. Patent No. 6,525,060 (the '060 Patent). In support of such Petition, Applicant provides the following information:

I. SIGNATURE REQUIREMENTS (37 C.F.R. §1.730)

A. IDENTIFICATION OF PERSON(S) SUBMITTING THE APPLICATION

I, Leonard C. Mitchard, represent that I am a registered practitioner (Registration No. 29,009) appointed by the patent owner of record.

B. RECORDAL OF ASSIGNMENT IN PTO

AstraZeneca UK Limited, a corporation organized under the laws of England, having its principal office and place of business in London, England, and appearing as the Assignee on the face of the '060 Patent, is the owner of the entire legal right, title and interest in and to the '060 Patent by virtue of an assignment from the named inventors David HARDERN, Anthony INGALL, Brian SPRINGTHORPE, Paul WILLIS and Simon GUILE, recorded in the United States Patent & Trademark Office ("USPTO") on March 8, 2000 at Reel/Frame 011067/0015-0017.

The assignment record for the '060 Patent contains an entry recorded on May 16, 2001 at Reel/Frames 011803/0983-0987 identified in the record as a "Change of Name" (hereinafter the Change of Name document). The recordal of the Change of Name document on May 16, 2001 was in error, as the name of AstraZeneca UK Limited was never changed to AstraZeneca AB. A Petition to Expunge the Change of Name document (copy of the Petition to Expunge attached hereto as **Exhibit 1**) has been submitted in the USPTO on September 8, 2011.

C. PROOF OF AUTHORIZATION OF SIGNATORY TO ACT AS AN AGENT ON BEHALF OF THE PATENT OWNER

Attached as **Exhibit 2** is a Power of Attorney establishing authorization of Leonard C. Mitchard to act as an agent on behalf of the patent owner.

II. APPLICATION REQUIREMENTS (37 C.F.R. §1.740)

A. IDENTIFICATION OF APPROVED PRODUCT (1.740(a)(1))

The United States Food and Drug Administration ("FDA") has approved New Drug Application ("NDA") No. 022433 for BRILINTA™. The active ingredient of BRILINTA is ticagrelor. A copy of the approved labeling is attached hereto as **Exhibit 3**.

Ticagrelor is identified by several names (depending on the naming convention used). Two names used are:

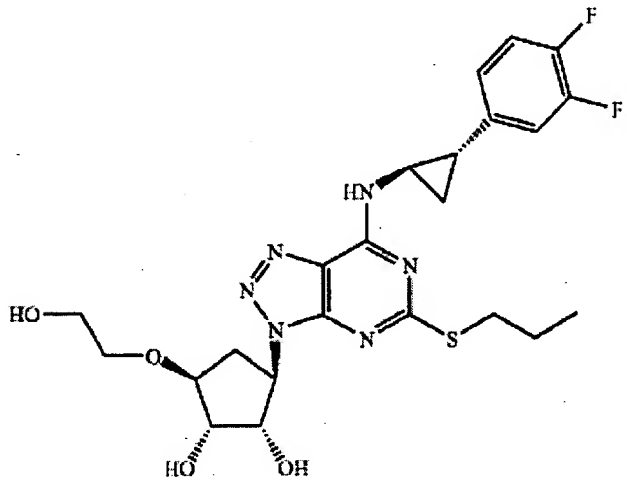
[1*S*-(1α, 2α, 3β (1*S**,2*R**),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol; and

(1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol.

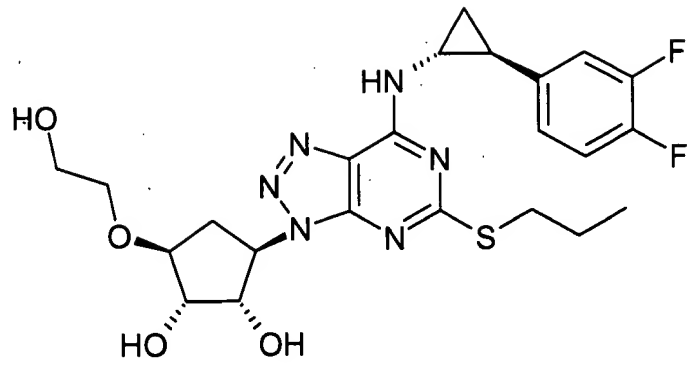
The empirical formula is $C_{23}H_{28}F_2N_6O_4S$.

The molecular weight is 522.57.

Ticagrelor can be represented by the following structural formulae:



and



Each tablet of BRILINTA contains 90 mg ticagrelor.

BRILINTA therapy should be initiated with a 180 mg oral loading dose (two – 90 mg tablets) and then continued at 90 mg twice daily.

BRILINTA is to be used in combination with aspirin. After an initial loading dose of aspirin (usually 325 mg.), BRILINTA is used with a daily maintenance dose of aspirin of 75 – 100 mg.

BRILINTA is a P2Y12 platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.

B. IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH REGULATORY REVIEW OCCURRED (1.740(a)(2))

Regulatory review for this product occurred under the Federal Food Drug & Cosmetic Act ("FDC Act") FDCA §505(b)(1), 21 U.S.C. §355(b)(1).

C. DATE OF APPROVAL (1.740(a)(3))

The FDA approved No. 022433 for BRILINTA for commercial marketing or use under §505 of the FDC Act on **July 20, 2011**.

D. IDENTIFICATION OF ACTIVE INGREDIENTS AND PREVIOUS APPROVAL INFORMATION (1.740(a)(4))

(1) BRILINTA™ is a human drug product, the sole active ingredient of which is ticagrelor, having the structure identified above.

(2) Neither ticagrelor, nor any salt or ester thereof, has been previously approved, alone or in combination, for commercial marketing or use under the Food, Drug & Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(3) BRILINTA™ is approved for commercial marketing under § 505(b)(1) of the FDCA (see BRILINTA™ approval letter attached as **Exhibit 4**).

(4) BRILINTA™ is approved for reducing the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction) (see BRILINTA™ approved labeling text attached as **Exhibit 3**).

E. TIMELY SUBMISSION OF APPLICATION (60 DAYS) (1.740(a)(5))

This application is being submitted within the sixty-day time period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last date this application may be submitted is September 16, 2011, assuming the date of approval is counted as day one, and further assuming that if a due date falls on a weekend, the application must be submitted on the last working day before that weekend.

F. IDENTIFICATION OF PATENT (1.740(a)(6), (7), (8))

Name of the Inventors: David HARDERN
Anthony INGALL
Brian SPRINGTHORPE
Paul WILLIS
Simon GUILE

Patent No. 6,525,060

Date of Issue: February 25, 2003

Date of Original Expiration: December 2, 2019

A copy of the patent, including the entire specification and claims is attached as **Exhibit 5**.

A copy of the U.S. Patent & Trademark Office Maintenance Fee Statement is attached as **Exhibit 6**.

No terminal disclaimer has been submitted for the '060 Patent.

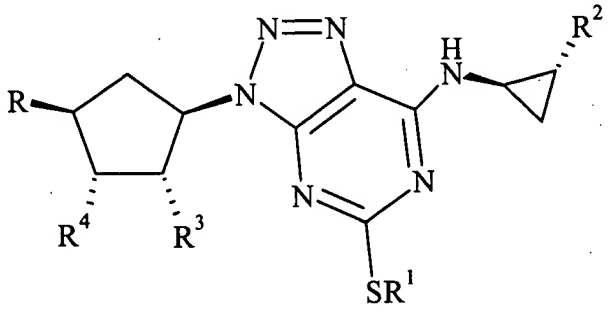
The '060 Patent has not been the subject of a reexamination proceeding.

G. IDENTIFICATION OF CLAIMS READING ON THE APPROVED PRODUCT (1.740(a)(9))

The statements below are made solely to comply with the requirements of 37 C.F.R. § 1. 740(a)(9). As the M.P.E.P. acknowledges, § 1.740(a)(9) does not require an applicant to show whether or how the listed claims would be infringed, and that this question cannot be answered without specific knowledge concerning acts performed by third parties. As such, these comments are not an assertion or an admission of Applicant as to the scope of the listed claims, or whether or how any of the listed claims would be infringed, literally or under the doctrine of equivalents, by the manufacture, use, sale, offer for sale, or importation of any product.

(1) Drug Substance.

The '060 Patent claims the active ingredient of the approved product which is ticagrelor. The '060 Patent includes 14 claims. Claim 1 (column 23, lines 14-39) describes a compound of formula (I):



(I)

wherein:
R^1 is C_{3-5} alkyl optionally substituted by one or more halogen atoms;
R^2 is a phenyl group, optionally substituted by one or more fluorine atoms;
R^3 and R^4 are both hydroxy;
R is XOH, where X is CH_2, OCH_2CH_2 or a bond;
or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt provided that:
when X is CH_2 or a bond, R^1 is not propyl;
when X is CH_2 and R^1 is $CH_2CH_2CF_3$, butyl or pentyl, the phenyl group at R^2 must be substituted by fluorine;
when X is OCH_2CH_2 and R^1 is propyl, the phenyl group at R^2 must be substituted by fluorine.

The specification of the '060 Patent also describes the substituents underlined above at column 2, lines 30-44.

Ticagrelor is within the scope described in claim 1 when R^1 is propyl (C_3 alkyl); R^2 is a phenyl group, optionally substituted by one or more (i.e., two) fluorine

atoms; R^3 and R^4 are both hydroxy; R is XOH, where X is OCH_2CH_2, provided that: when X is OCH_2CH_2 and R^1 is propyl, the phenyl group at R^2 must be substituted by fluorine.

Therefore, ticagrelor is covered by claim 1 of the '060 Patent.

Ticagrelor is also within the scope of dependent claims 2, 3 and 4 (column 23, lines 40-45) of the '060 Patent for the reasons described above for claim 1.

Claim 5 names, as the third named compound (column 23, lines 55-58), the compound [1*S*-(1α, 2α, 3β (1*S**,2*R**),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol which refers to a compound having the structure of ticagrelor.

Therefore ticagrelor is covered by claim 5 of the '060 Patent.

Example 3 in the specification of USPN 6525060, at column 13, line 54 to column 16, line 18, describes the synthesis of [1*S*-(1α, 2α, 3β (1*S**,2*R**),5β]-3-[7-[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol.

(2) Drug Product (Composition/Formulation). 37 C.F.R. § 1.740(a)(9)(i)

Claim 6 of the '060 Patent (column 24, line 16-18) describes a pharmaceutical composition comprising a compound according to claim 1 in combination with a pharmaceutically acceptable diluent, adjuvant and/or carrier.

As set forth above, ticagrelor is within the scope described in claim 1, and BRILINTA, 90 mg., Tablet, contains mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow (*See Label, Description*). Such ingredients are pharmaceutically acceptable diluents, adjuvants or carriers. BRILINTA is thus within the scope of a pharmaceutical composition of claim 6 of the '060 Patent.

Therefore, a 90 mg. Tablet of BRILINTA is covered by claim 6 of the '060 Patent.

(3) Method of Use. 37 C.F.R. § 1.740(a)(9)(ii)

Claim 7 of the '060 Patent (column 24, line 19-22) describes a method of treatment of post-myocardial infarction which comprises administering to a patient suffering therefrom a therapeutically effective amount of a compound according to claim 1. The Label (see **Exhibit 3**) identifies an indication to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction).

Therefore, claim 7 of the '060 Patent covers an indication of BRILINTA in a 90 mg., tablet form.

H. RELEVANT DATES AND INFORMATION (1.740(a)(10))

The '060 Patent claims a human drug.

The '060 Patent issued on February 25, 2003.

The effective date of the investigational new drug (IND) application (received by the Federal Drug Administration (FDA) on April 29, 2003) was May 29, 2003 (30 days after the receipt date), which is after the February 25, 2003 grant of the patent. The IND No. is 65808.

The new drug application (NDA) was submitted on November 13, 2009 and was received by the FDA on November 16, 2009. The NDA No. is 022433.

The NDA was approved on July 20, 2011.

I. BRIEF DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW (1.740(a)(11))

The Table below presents a brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

CHRONOLOGY OF SIGNIFICANT ACTIVITIES: IND No. 65,808 AND NDA No. 22-433		
Application No.	Date	Description
	05 Dec-02	Pre-IND Meeting.
IND 65,808	28 April-03	Submission of IND 65,808
IND 65,808	14 May 03	AZ receives a letter from FDA, dated May 9, 2003 with date of receipt for IND 65,808 of April 29, 2003
IND 65,808	17 Mar-04	Request for SPA for the 2-year carcinogenicity studies
IND 65,808	25 May-04	DISPERSE Meeting (Type C) to discuss study results and guidance for design of DISPERSE2
IND 65,808	08 Dec-05	EoP2 Meeting. Briefing document was submitted on 11 Nov-05.
IND 65,808	20 Jan-06	Phase 3 Population PK Plan submission as requested by the FDA at the EoP2 meeting.
IND 65,808	14 Dec-07	AZ submits a request for SPA for RESPOND
IND 65,808	16 Jan-09	QbD Meeting
IND 65,808	28 Jan-09	QTc teleconference
IND 65,808	14 Apr-09	Final PLATO SAP submission. Changes from the draft PLATO SAP (submitted 27 Aug-08).
IND 65,808	20 Apr-09	Pre-NDA Meeting. Briefing document was submitted on 18 Mar-09.
IND 65,808	22 July-09	Pre-NDA Response Document submitted to agree several outstanding items from the pre-NDA meeting.
IND 65,808	05 Aug-09	PLATO Results Meeting. Slides were submitted on 30 July-09.
NDA 22-433	13 Nov-09	Submission of NDA 22-433
NDA 22-433	24 Nov 09	AZ receives a NDA acknowledgment letter from FDA, dated November 24, 2009 with date of receipt for NDA 22-433 of November 16, 2009

NDA 22-433	19 Nov-09	FDA e-mail IR for clopidogrel and PLATO studies. Responses provided on 19, 20 and 24 Nov-09.
NDA 22-433	24 Nov-09	FDA e-mail IR for PLATOAUD file size and number of records. AZ responded 25 Nov-09.
NDA 22-433	25 Nov-09	FDA e-mail IR for PLATO clinical site dataset. AZ responded 18 Dec-09.
NDA 22-433	30 Nov-09	FDA e-mail IR for location of nonclinical reports. AZ responded 2 Dec-09.
NDA 22-433	4 Dec-09	FDA e-mail IR for summary of intermediate code changes during development. AZ responded 4 Dec-09.
NDA 22-433	4 Dec-09	FDA e-mail IR for clinical site information: 3 Hungary & 3 Poland. AZ responded 4 Dec-09.
NDA 22-433	7 Dec-09	FDA e-mail IR for PLATO protocol and additional CRFs. AZ responded 14, 16 and 17 Dec -09.
NDA 22-433	10 Dec-09	FDA teleconference to discuss Medwatch forms. AZ responded 18 Dec-09.
NDA 22-433	16 Dec-09	FDA e-mail IR for location of Nonclinical study. AZ responded 18 Dec-09.
NDA 22-433	17 Dec-09	FDA teleconference to discuss the impurity code designations. AZ responded 18 Dec-09.
NDA 22-433	17 Dec-09	FDA e-mail IR for aspirin dataset information. AZ responded 17 Dec-09.
NDA 22-433	21 Dec-09	FDA e-mail IR for PK data for 2 SAD studies. AZ responded 24 Dec-09.
NDA 22-433	13 Jan-10	FDA e-mail IR for update on aspirin interaction in PLATO. AZ responded 15 Feb, 15 Mar and 30 Apr-10.
NDA 22-433	26 Jan-10	FDA IR for CMC dissolution data. AZ responded 16, 26 Feb, and 5 Mar-10.
NDA 22-433	3 Feb-10	FDA e-mail IR for aspirin dataset. AZ responded 15 Feb-10.
NDA 22-433	25 Feb-10	FDA e-mail IR for concomitant meds clarification. AZ responded 3 Mar-10.
NDA 22-433	4 Mar-10	FDA e-mail IR for location of CSR16 in NDA. AZ responded 4 Mar-10.
NDA 22-433	5 Mar-10	FDA e-mail IR for PLATO: explanation of non-antithrombotic meds/ITT/STENTFL. AZ responded 22 Mar-10.
NDA 22-433	11 Mar-10	FDA e-mail IR for PLATO dataset. AZ responded 18 Mar-10.
NDA 22-433	15 Mar-10	FDA e-mail IR for genotoxicity for UL134 and UL111. AZ responded 16 and 25 Mar-10.
NDA 22-433	18 Mar-10	FDA e-mail IR for CYP2C19 genotype data. AZ responded 16 May-10.
NDA 22-433	25 Mar-10	FDA e-mail IR for SAP/protocol clarifications. AZ responded 12 Apr-10.

NDA 22-433	12 Apr-10	FDA teleconference to discuss fatal bleeds in PLATO. IR for PLATO. AZ responded 12 Apr-10.
NDA 22-433	16 Apr-10	FDA teleconference to discuss the PLATO study close-out
NDA 22-433	22 Apr-10	FDA e-mail IR for ademog.xpt. AZ responded 7 May-10.
NDA 22-433	4 May-10	FDA e-mail IR for explanation of variables. AZ responded 12 May-10.
NDA 22-433	11 May-10	FDA teleconference to discuss the impurity AZ13232789.
NDA 22-433	12 May-10	FDA e-mail IR for Holter substudy Table-All Patients. AZ responded 13 May-10.
NDA 22-433	12 May-10	FDA e-mail IR for Exposure calculations for AZ13232789. AZ responded 21 May-10.
NDA 22-433	13 May-10	FDA e-mail IR for CMC questions for DS and DP. AZ responded 4 Jun-10.
NDA 22-433	18 May-10	FDA e-mail IR for gynecomastia. AZ responded 28 May-10.
NDA 22-433	25 May-10	FDA e-mail IR for study report shift tables. AZ responded 27 May-10.
NDA 22-433	26 May-10	FDA e-mail IR for serum electrolyte data sets. AZ responded 2 Jun-10.
NDA 22-433	27 May-10	FDA e-mail IR for stent thrombosis. AZ responded 4 Jun-10.
NDA 22-433	1 Jun-10	FDA e-mail IR for CRFs. AZ responded 3 Jun-10.
NDA 22-433	4 Jun-10	FDA e-mail IR for asa and endpoint. AZ responded 15 Jun-10.
NDA 22-433	7 Jun-10	FDA e-mail IR for reports for AR-C133913XX (AZ11879477). AZ responded 11 Jun-10.
NDA 22-433	7 Jun-10	Face-to-face meeting with FDA to discuss PLATO North American interaction and Ad Com preparations.
NDA 22-433	8 Jun-10	FDA e-mail IR for asa and stent thrombosis. AZ responded 16, 17, 21 and 29 Jun-10.
NDA 22-433	9 Jun-10	FDA teleconference to clarify FDA IR received 8 Jun. IR for stent. AZ responded 21 Jun-10.
NDA 22-433	10 Jun-10	FDA teleconference to discuss the prolactin hypothesis. AZ responded 16 Jul-10.
NDA 22-433	18 Jul-10	FDA teleconference to discuss the ASA and the Ad Com
NDA 22-433	7 Jul-10	FDA Teleconference: IR awcadj.xpt dataset definitions and CABG figure. AZ responded 16 Jun-10.
NDA 22-433	8 Jul-10	FDA teleconference to discuss the Ad Com and AZ13232789

NDA 22-433	12 Jul-10	FDA IR for AZ13232789 genotoxicity data. AZ responded 23 Jul-10.
NDA 22-433	14 Jul-10	FDA teleconference to discuss CMC dissolution: IR updated specification. AZ responded 16 Jul-10.
NDA 22-433	15 Jul-10	FDA e-mail IR for study conduct. AZ responded 22 Jul-10.
NDA 22-433	19 Jul-10	FDA e-mail IR for asa dose. AZ responded 22 Jul-10.
NDA 22-433	19 Jul-10	FDA e-mail IR for Updated Drug Product Specification. AZ responded 20 Jul-10.
NDA 22-433	21 Jul-10	FDA teleconference to discuss the information request received 15 Jul-10.
NDA 22-433	21 Jul-10	FDA e-mail IR for randomization time. AZ responded 22 Jul-10.
NDA 22-433	22-Jul-10	FDA teleconference to discuss the Ad Com slides
NDA 22-433	23 Jul-10	FDA e-mail IR for AZ historical control data for eCAC. AZ responded 26 Jul-10.
NDA 22-433	23 Jul-10	FDA e-mail IR for eCAC references. AZ responded 27 Jul-10.
NDA 22-433	23 Jul-10	FDA Teleconference: IR for update drug product specification. AZ responded 26 Jul-10.
NDA 22-433	26 Jul-10	FDA e-mail IR for CoA for AZ13232789. AZ responded 29 Jul-10.
NDA 22-433	28 Jul-10	FDA e-mail IR for drug substance specification. AZ responded 30 Jul-10.
NDA 22-433	28 Jul-10	FDA e-mail IR for CMC methods. AZ responded 4 Aug-10.
NDA 22-433	28 Jul-10	Advisory Committee Meeting to review NDA 22-433
NDA 22-433	30 Jul-10	FDA e-mail IR for post Ad Com. AZ responded 6 Aug-10.
NDA 22-433	6 Aug-10	FDA e-mail IR for PLATO and OFFSET study information. AZ responded 11 Aug-10.
NDA 22-433	11 Aug-10	FDA e-mail IR for lost to follow-up dataset. AZ responded 13 Aug-10.
NDA 22-433	13-Aug-10	FDA IR on the draft carton and container labeling. AZ responded on 24 Aug-10.
NDA 22-433	16 Aug-10	FDA teleconference to discuss the NDA review
NDA 22-433	17 Aug-10	FDA e-mail IR for datasets and programs for PLATO. AZ responded 18, 19, 20 Aug-10.
NDA 22-433	20 Aug-10	FDA e-mail IR for asa whether enteric coated. AZ responded 20 Aug-10.

NDA 22-433	27 Aug-10	FDA e-mail comments on selected sections of the ticagrelor labeling. AZ responded on 31 Aug-10.
NDA 22-433	1 Sept-10	FDA face to face meeting. AZ provided Mechanistic Hypothesis on Interaction with ASA Dose in PLATO on 8 Sept-10
NDA 22-433	1 Oct-10	AZ submission of summary of apolipoprotein data from PLATO blood core sub-study
NDA 22-433	16 Dec-10	FDA e-mail with complete response letter. AZ response on 20 Jan-11.
NDA 22-433	21 Dec-10	AZ submission of proposal for responding to the Complete Response Letter, received 16 Dec-10.
NDA 22-433	22 Jan-11	FDA OSE e-mail request for resubmission of the proposed proprietary name. AZ response on 24 Jan-11
NDA 22-433	2 Feb-11	FDA e-mail IR for statistical and clinical questions. AZ response on 17 Feb-11, 18 Feb-11 and 23 Feb-11.
NDA 22-433	3 Feb-11	FDA e-mail IR for patient event handling. AZ response on 17 Feb-11.
NDA 22-433	19 Feb-11	FDA e-mail comment on Median55. AZ provided a response on 23 Feb-11.
NDA 22-433	24 Feb-11	FDA teleconference. AZ provided additional requests for information on 8 Mar-11.
NDA 22-433	4 Mar-11	FDA e-mail IR on audit file. AZ provided responses on 11 Mar-11 and 16-Mar 11.
NDA 22-433	9 Mar-11	FDA teleconference on aspirin mechanism. AZ provided background information (slides and references) on 7 Mar-11.
NDA 22-433	11 Mar-11	FDA e-mail IR on adjudication. AZ responses on 18 Mar-11, 22 Mar-11 and 25 Mar-11.
NDA 22-433	25 Mar-11	FDA e-mail IR on adjudication. AZ response on 1 Apr-11.
NDA 22-433	31 Mar-11	FDA e-mail IR for preclinical. AZ response on 31 Mar-11.
NDA 22-433	1 Apr-11	FDA e-mail IR for adjudication. AZ response on 8 Apr-11.
NDA 22-433	8 Apr-11	FDA e-mail IR for REMS and clinical information. AZ responded on 15 Apr-11 and 19 Apr-11.
NDA 22-433	12 Apr-11	FDA e-mail IR for safety reporting. AZ response on 14 Apr-11.
NDA 22-433	13 Apr-11	FDA e-mail IR for blister label. AZ provided cross reference response on 2 May-11 to 24 Aug-10 label response.
NDA 22-433	15 Apr-11	FDA e-mail IR for work orders. AZ response on 4 May-11.
NDA 22-433	20 Apr-11	Mid cycle review face to face meeting with FDA.
NDA 22-433	22 Apr-11	FDA e-mail IR for datasets. AZ response on 5 May-11.

NDA 22-433	13 May-11	FDA e-mail IR with label comments. AZ response on 23 May-11.
NDA 22-433	13 May-11	FDA e-mail IR for safety reporting. AZ response on 2 Jun-11.
NDA 22-433	26 May-11	FDA e-mail IR concerning DSMB. AZ response on 3 Jun-11.
NDA 22-433	6 Jul-11	AZ submits draft label.
NDA 22-433	7 Jul-11	FDA e-mail comments for REMS. Additional comments received 11 Jul-11. AZ provided responses on 13 Jul-11.
NDA 22-433	12 Jul-11	FDA e-mail IR for dataset. AZ responded on 14 Jul-11.
NDA 22-433	14 Jul-11	AZ submits draft label.
NDA 22-433	20 Jul-11	FDA issues approval letter for NDA 22-433

J. STATEMENT THAT APPLICANT IS ELIGIBLE FOR EXTENSION (1.740(a)(12))

In the opinion of the Applicant, the '060 Patent is eligible for extension. In the opinion of the Applicant, the '060 Patent is entitled to an extension of **1794 days**, setting the patent to expire on **October 30, 2024**.

The following are the calculations, made in accordance with 37 C.F.R. § 1.775, that result in the claimed extension:

(1) The testing phase, as calculated according to 37 C.F.R. § 1.775(c)(1), began on May 29, 2003 (the effective date of the IND is 30 days after the date of receipt, April 29, 2003) and ended on November 16, 2009 (the day of receipt by the FDA of the NDA). Thus, the testing phase is **2364 days**.

(2) The approval phase, as calculated according to 37 C.F.R. § 1.775(c)(2), began on November 16, 2009 (day of receipt by the FDA of the NDA) and ended on July 20, 2011, when approval was granted. Thus, the approval phase is **612 days.**[1]

(3) According to 37 C.F.R § 1.775(c) the length of the Regulatory Review Period (**RRP**) is the sum of the numbers obtained in §§ 1.775(c)(1), **2364 days**, and (c)(2), **612 days**. Thus the **RRP** is **2364 + 612 = 2976 days.**

(4) The Patent Term Extension, as set forth in 37 C.F.R § 1.775(d)(1), is determined by **subtracting from the RRP (2976 days** as calculated above) the following number of days as set forth in (i), (ii), and (iii) immediately below:

(i) *The number of days in the RRP which were on or before the date the patent issued.* The patent issued on February 25, 2003, before initiation of the entire RRP. Accordingly, **no days are subtracted from the RRP** under this paragraph. *See* 37 C.F.R. § 1.775(d)(1)(i).

(ii) *The number of days applicant did not act with due diligence.* Applicant acted with due diligence throughout the entire regulatory review period. **No days are subtracted from the RRP under this paragraph**. *See* 37 C.F.R. § 1.775(d)(1)(ii).

(iii) *One-half the number of days remaining in the testing period, which was calculated as 2364 above, after reducing the number of days in accordance with paragraphs (i) and (ii) above (ignoring half days for subtraction).* As noted above, there were no days under both (i) and (ii) above. Thus one-half of 2364 in this section (iii) = **1182 days that will be subtracted from the RRP**. *See* 37 C.F.R. § 1.775(d)(1)(iii).

[1] Please note that November 16, 2009 is double counted according to C.F.R. § 1.775(c): once in the testing phase and once in the approval phase.

(5) The resultant number of days of patent term extension: **2976 - 0 - 0 - 1182 = 1794 days of extension.**

(6) The original patent term for the '060 patent ends December 2, 2019.

(7) Addition of the extension of **1794 days** to the end of the original patent term (using December 3, 2019 as day one of the extension) extends the expiration date of the patent to **October 30, 2024.**

(8) Fourteen years from the approval date of the product (July 20, 2011) is July 20, 2025.

(9) Pursuant to 35 U.S.C. §156(c)(3), the extended term of the patent cannot exceed 14 years from the date of product approval. The fourteen year cap does not apply since the extension of 1794 days sets the patent to expire on **October 30, 2024**, which is before the date that is 14 years post-approval (July 20, 2025).

(10) Pursuant to 35 U.S.C. §156(g)(6)(A), the extension period is subject to a five year limitation (for patents issued after September 24, 1984). The five year limitation does not apply since the patent term extension of **1794** days extends to **October 30, 2024**, which is less than five years (the five year date being December 2, 2024).

(11) In light of the calculations set forth above, the extended expiration date of the '060 Patent is believed to be **October 30, 2024.**

K. ACKNOWLEDGEMENT OF DUTY OF DISCLOSURE (1.740(a)(13))

I, Leonard C. Mitchard, the person signing below, acknowledge the duty to disclose to the Director of the U.S. Patent and Trademark Office and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension which is being sought herein.

L. FEE (1.740(a)(14))

The requisite fee of $1120.00 (37 C.F.R. §1.20(j)) is submitted herewith. The Commissioner is authorized to charge any deficiency in the fee submitted, or credit any overpayment, to Deposit Account No. 14-1140 under docket number **3764-205**.

M. CORRESPONDENCE

Please direct all inquiries and correspondence relating to this application to:

Leonard C. Mitchard, Esq.
NIXON & VANDERHYE P.C.
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

N. COPIES (1.740(b))

Four additional copies of this application are attached, making a total of five copies being submitted.

O. POWER OF ATTORNEY (1.730(a)(2) and (d))

The undersigned is authorized to act on behalf of the Applicant by virtue of the signed Power of Attorney submitted herewith as **Exhibit 2**.

CONCLUSION

In conclusion, on the basis of the information provided herein, Applicant respectfully asserts that the '060 Patent is entitled to the requested **1794** day extension of its term to **October 30, 2024**.

Prompt action on this application is respectfully requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /Leonard C. Mitchard/
Leonard C. Mitchard
Reg. No. 29,009
Agent for the Patent Owner

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Arlington, VA 22203-1808
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent 6,525,060

HARDERN et al.

Issued: February 25, 2003

Filed: March 8, 2000;

Atty. Ref.: LCM-3764-205

TC/A.U.: 1624 Conf. No.: 2221

Examiner: Ford, J.M.

For: TRIAZOLO(4,5-D)PYRIMIDINE COMPOUNDS

* * * * * * * * * * *

September 8, 2011

Office of Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO EXPUNGE DOCUMENTS UNDER 37 C.F.R. §1,182

Petition is hereby made under 37 C.F.R. §1.182 to expunge documents recorded in the assignment record against U.S. Patent No. 6,525,060 on May 16, 2001 at Reel/Frame 011803/0983-0987. The "Conveyance" is identified as a "Change of Name", and the "Assignee" is identified as AstraZeneca AB. The expungement is requested to correct the record against U.S. Patent No. 6,525,060 as the correct owner is AstraZeneca UK Limited, and AstraZeneca UK Limited has never changed its name to AstraZeneca AB. The error was unintentional.

The petition fee of $400.00, as set forth in 37 C.F.R. §1.17(f) is submitted with this filing. The Commissioner is authorized to charge any further fee that may be required, or credit any overpayment, to our Deposit Account No. **14-1140** under Docket 3764-205.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /Leonard C. Mitchard/

Leonard C. Mitchard
Reg. No. 29,009

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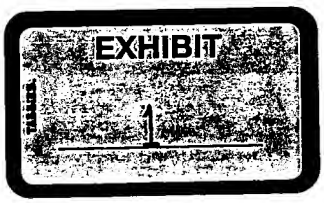


IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent 6,525,060

HARDERN et al. Atty. Ref.: 3764-205; Confirmation No. 2221

Appl. No. 09/508,195 TC/A.U. 1624; Issued: February 25, 2003

Filed: March 8, 2000 Examiner: Ford, J.M.

For: TRIAZOLO(4,5-D)PYRIMIDINE COMPOUNDS

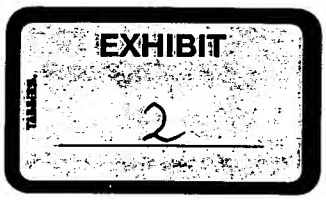
* * * * * * * * * * * *

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

POWER OF ATTORNEY

AstraZeneca UK Limited, the assignee of the entire legal right, title and interest in US Patent 6,525,060, hereby appoints the attorneys of **Customer Number 23117** individually and collectively its agent to prosecute the present application for patent term extension, and to transact all business in the Patent and Trademark Office in connection therewith.

Please direct correspondence for this application to the address associated with **Customer Number 23117**. Please direct telephone calls to Leonard C. Mitchard at (703) 816-4005.



1854446

Certificate Under 37 C.F.R. §3.73(b)

AstraZeneca UK Limited, a corporation having a place of business at 2 Kingdom Street, London UK W2 6BD , hereby states that it is the assignee of the entire legal right, title and interest in the patent identified above by virtue of an assignment from the inventors to the aforesaid assignee recorded at the United States Patent Office on March 8, 2000 at reel 011067, frame 0015.

The undersigned (whose title is typed below) is empowered to sign this statement on behalf of the assignee.

AstraZeneca UK Limited

By: _____

07-SEPTEMBER-2011
Date

Name: DR ALLEN FILES

Title: AUTHORISED REPRESENTATIVE

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BRILINTA safely and effectively. See full prescribing information for BRILINTA.

BRILINTA™ (ticagrelor) tablets, for oral use
Initial U.S. Approval: 2011

WARNING: BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).**

——————INDICATIONS AND USAGE——————

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis. (1)

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily. (1, 5.2, 14).

——————DOSAGE AND ADMINISTRATION——————

- Initiate treatment with 180 mg (two 90 mg tablets) oral loading dose. (2)
- Continue treatment with 90 mg twice daily. (2)
- After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. (2)

——————DOSAGE FORMS AND STRENGTHS——————

- 90 mg tablets (3)

——————CONTRAINDICATIONS——————

- History of intracranial hemorrhage (4.1)
- Active pathological bleeding (4.2)
- Severe hepatic impairment (4.3)

——————WARNINGS AND PRECAUTIONS——————

- Like other antiplatelet agents, BRILINTA increases the risk of bleeding. (5.1)
- In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. (5.2, 14)
- Moderate Hepatic Impairment: Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor. (5.3)
- Dyspnea: Dyspnea was reported more frequently with BRILINTA than with clopidogrel. Dyspnea resulting from BRILINTA is self-limiting. Rule out other causes. (5.4)
- Discontinuation of BRILINTA: Premature discontinuation increases the risk of myocardial infarction, stent thrombosis, and death. (5.5)

——————ADVERSE REACTIONS——————

Most common adverse reactions are bleeding 12% and dyspnea 14%. (5.1, 5.4, 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

——————DRUG INTERACTIONS——————

- Avoid use with strong CYP3A inhibitors or CYP3A inducers. (7.1, 7.2).
- Patients receiving more than 40 mg per day of simvastatin or lovastatin may be at increased risk of statin-related adverse effects. (7.3)
- Monitor digoxin levels with initiation of or any change in BRILINTA. (7.4)

See 17 For PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5. 2, 14).**

1 INDICATIONS AND USAGE

Acute Coronary Syndromes

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis *[see Clinical Studies (14)]*.

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily *[see Warnings and Precautions (5.2) and Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily

After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg.

ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA.

BRILINTA can be administered with or without food.

A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

3 DOSAGE FORMS AND STRENGTHS

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a "90" above "T" on one side.

4 CONTRAINDICATIONS

4.1 History of Intracranial Hemorrhage

BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population *[see Clinical Studies (14)]*.

4.2 Active Bleeding

BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

4.3 Severe Hepatic Impairment

BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins *[see Clinical Pharmacology (12.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 General Risk of Bleeding

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased *[see Adverse Reactions (6.1)]*.

In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures, and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDS]).

When possible, discontinue BRILINTA five days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding.

If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.

5.2 Concomitant Aspirin Maintenance Dose

In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg *[see Dosage and Administration (2) and Clinical Studies (14)]*.

5.3 Moderate Hepatic Impairment

BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

5.4 Dyspnea

Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption.

In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV_1. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

5.5 Discontinuation of BRILINTA

Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

5.6 Strong Inhibitors of Cytochrome CYP3A

Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

5.7 Cytochrome CYP3A Potent Inducers

Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital *[see Drug Interactions (7.2), and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following adverse reactions are also discussed elsewhere in the labeling:

- Dyspnea *[see Warnings and Precautions (5.4)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

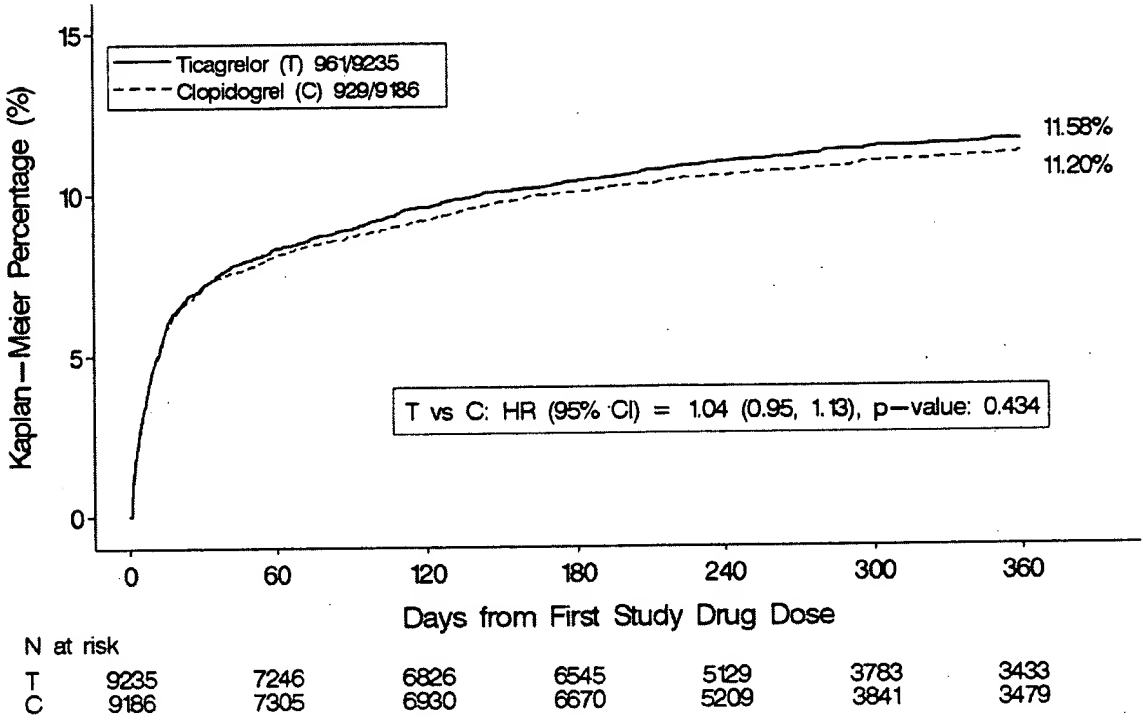
BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

Bleeding
PLATO used the following bleeding severity categorization:

- Major bleed – fatal/life-threatening. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.
- Major bleed – other. Any one of the following: significantly disabling (e.g., intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- Minimal bleed. All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

Figure 1 - Kaplan-Meier estimate of time to first PLATO-defined 'Total Major' bleeding event



Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days.

Table 1 - Non-CABG related bleeds (KM%)

	BRILINTA N=9235	Clopidogrel N=9186
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel.

In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

Table 2 –CABG bleeds (KM%)

	Patients with CABG	
	BRILINTA N=770	**Clopidogrel N=814**
Total Major	85.8	86.9
Fatal/Life-threatening	48.1	47.9
Fatal	0.9	1.1

Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in *in vitro* tests and BRILINTA is a reversibly binding $P2Y_{12}$ inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel.

No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

Drug Discontinuation

In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients.

Common Adverse Events

A variety of non-hemorrhagic adverse events occurred in PLATO at rates of 3% or more. These are shown in Table 3. In the absence of a placebo control, whether these are drug related cannot be determined in most cases, except where they are more common on BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

Table 3 – Percentage of patients reporting non-hemorrhagic adverse events at least 3% or more in either group

	BRILINTA N=9235	Clopidogrel N=9186
Dyspnea[a]	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Non-cardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

[a]Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal

Bradycardia

In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively.

In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

Gynecomastia

In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel.

Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the two treatment groups in PLATO.

Lab abnormalities

Serum Uric Acid:

Serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA and approximately 0.2 mg/dL on clopidogrel in PLATO. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group).

Serum Creatinine:

In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

7 DRUG INTERACTIONS

Effects of other drugs

Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.

7.1 CYP3A inhibitors

Avoid use of strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir and telithromycin) *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*.

7.2 CYP3A inducers

Avoid use with potent inducers of CYP3A (e.g., rifampin, dexamethasone, phenytoin, carbamazepine and phenobarbital) *[see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)]*.

7.3 Aspirin

Use of BRILINTA with aspirin maintenance doses above 100 mg reduced the effectiveness of BRILINTA *[see Warnings and Precautions (5.2) and Clinical Studies (14)]*.

Effect of BRILINTA on other drugs

Ticagrelor is an inhibitor of CYP3A4/5 and the P-glycoprotein transporter.

7.4 Simvastatin, lovastatin

BRILINTA will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg *[see Clinical Pharmacology (12.3)]*.

7.5 Digoxin

Digoxin: Because of inhibition of the P-glycoprotein transporter, monitor digoxin levels with initiation of or any change in BRILINTA therapy *[see Clinical Pharmacology (12.3)]*.

7.6 Other Concomitant Therapy

BRILINTA can be administered with unfractionated or low-molecular-weight heparin, GPIIb/IIIa inhibitors, proton pump inhibitors, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no adequate and well-controlled studies of BRILINTA use in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. BRILINTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. The lowest dose was approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m^2 basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m^2 basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of pelvis, and misshapen/misaligned sternebrae. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m^2 basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae occurred.

In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 180 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m^2 basis). Relatively minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m^2 basis).

8.3 Nursing Mothers

It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from BRILINTA, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of BRILINTA in pediatric patients have not been established.

8.5 Geriatric Use

In PLATO, 43% of patients were ≥65 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups.

No overall differences in safety or effectiveness were observed between these patients and younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

BRILINTA has not been studied in the patients with moderate or severe hepatic impairment. Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Hence, BRILINTA is contraindicated for use in patients with severe hepatic impairment and its use should be considered carefully in patients with moderate hepatic impairment. No dosage adjustment is needed in patients with mild hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied *[see Clinical Pharmacology (12.3)]*.

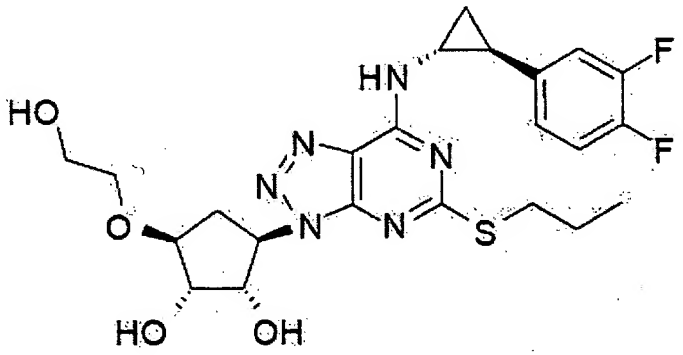
10 OVERDOSAGE

There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken.

Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.

11 DESCRIPTION

BRILINTA contains ticagrelor, a cyclopentyltriazolopyrimidine, inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP-receptor. Chemically it is (1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol. The empirical formula of ticagrelor is $C_{23}H_{28}F_2N_6O_4S$ and its molecular weight is 522.57. The chemical structure of ticagrelor is:



Ticagrelor is a crystalline powder with an aqueous solubility of approximately 10 μg/mL at room temperature.

BRILINTA tablets for oral administration contain 90 mg of ticagrelor and the following ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ticagrelor and its major metabolite reversibly interact with the platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

12.2 Pharmacodynamics

The inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6 week study examining both acute and chronic platelet inhibition effects in response to 20 μM ADP as the platelet aggregation agonist.

The onset of IPA was evaluated on Day 1 of the study following loading doses of 180 mg ticagrelor or 600 mg clopidogrel. As shown in Figure 2, IPA was higher in the ticagrelor group at all time points. The maximum IPA effect of ticagrelor was reached at around 2 hours, and was maintained for at least 8 hours.

The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, again in response to 20 μM ADP.

As shown in Figure 3, mean maximum IPA following the last dose of ticagrelor was 88% and 62% for clopidogrel. The insert in figure 3 shows that after 24 hours, IPA in the ticagrelor group (58%) was similar to IPA in clopidogrel group (52%), indicating that patients who miss a dose of ticagrelor would still maintain IPA similar to the trough IPA of patients treated with clopidogrel. After 5 days, IPA in the ticagrelor group was similar to IPA in the placebo group. It is not known how either bleeding risk or thrombotic risk track with IPA, for either ticagrelor or clopidogrel.

Figure 2 - Mean inhibition of platelet aggregation (±SE) following single oral doses of placebo, 180 mg ticagrelor, or 600 mg clopidogrel

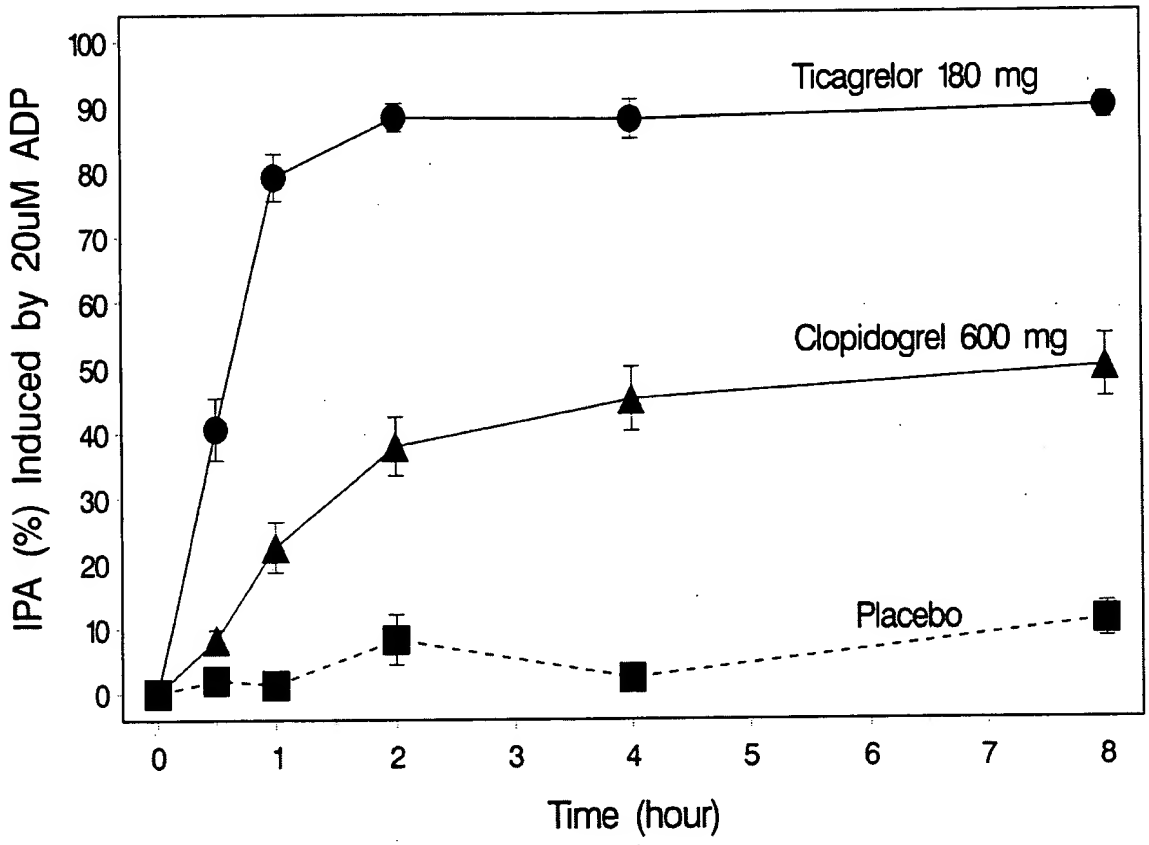
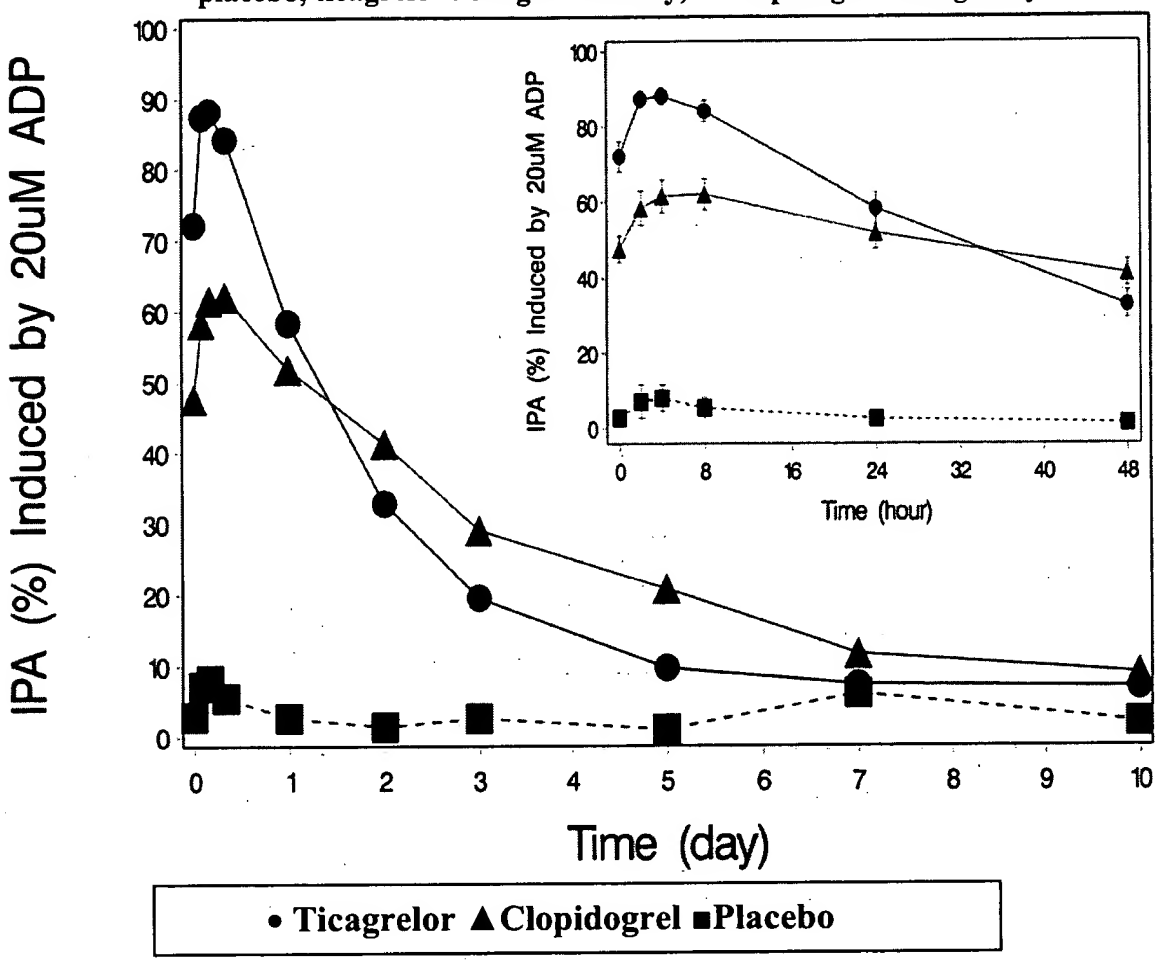


Figure 3 - Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily



Transitioning from clopidogrel to BRILINTA resulted in an absolute IPA increase of 26.4% and from BRILINTA to clopidogrel resulted in an absolute IPA decrease of 24.5%. Patients can be transitioned from clopidogrel to BRILINTA without interruption of antiplatelet effect *[see Dosage and Administration (2)]*.

12.3 Pharmacokinetics

Ticagrelor demonstrates dose proportional pharmacokinetics, which are similar in patients and healthy volunteers.

Absorption

Absorption of ticagrelor occurs with a median t_{max} of 1.5 h (range 1.0–4.0). The formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor occurs with a median t_{max} of 2.5 h (range 1.5-5.0).

The mean absolute bioavailability of ticagrelor is about 36%, (range 30%-42%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max}, but resulted in a 21% increase in AUC. The C_{max} of its major metabolite was decreased by 22% with no change in AUC. BRILINTA can be taken with or without food.

Distribution

The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and the active metabolite are extensively bound to human plasma proteins (>99%).

Metabolism

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30-40% of the exposure of ticagrelor.

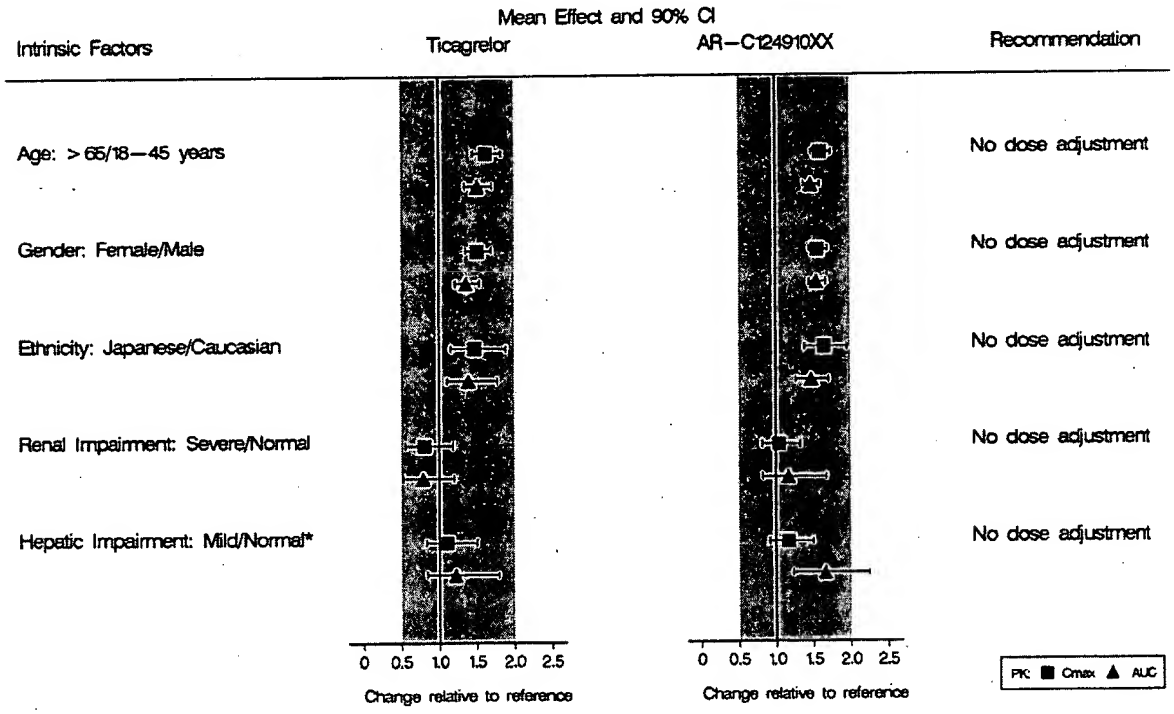
Excretion

The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean $t_{1/2}$ is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

Special Populations

The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in Figure 4. Effects are modest and do not require dose adjustment.

Figure 4 – Impact of intrinsic factors on the pharmacokinetics of ticagrelor



*BRILINTA has not been studied in patients with moderate or severe hepatic impairment.

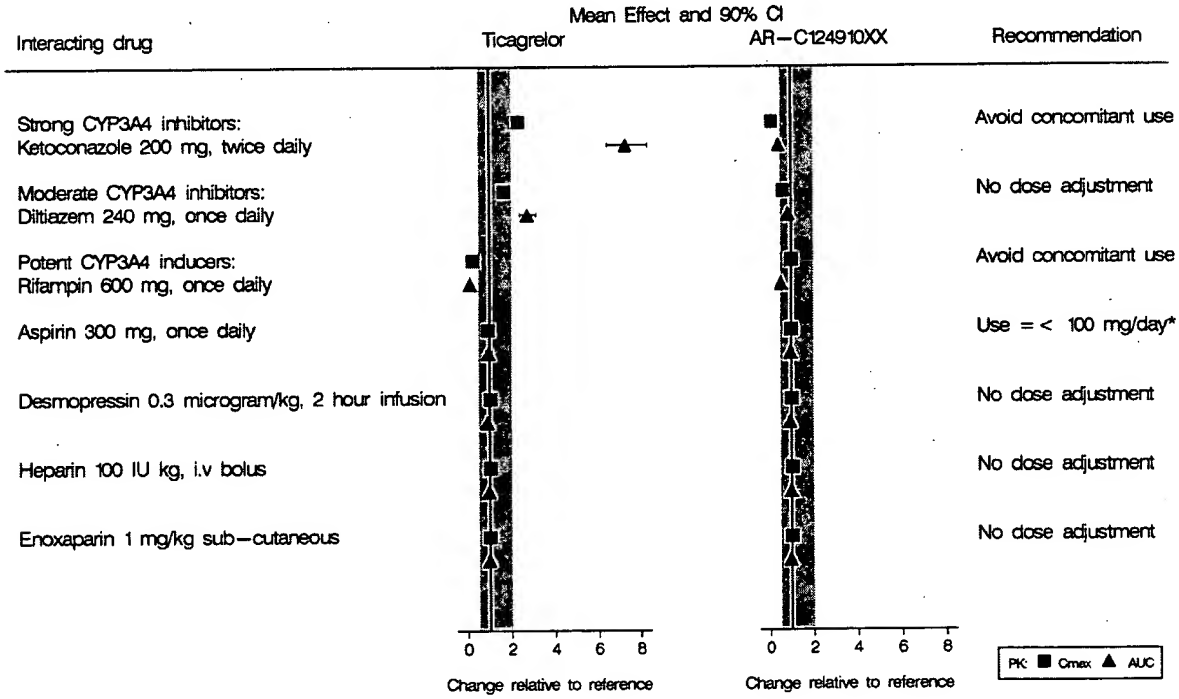
Pediatric
Ticagrelor has not been evaluated in a pediatric population *[see Use in Specific Populations (8.4)]*.

Body Weight
No dose adjustment is necessary for ticagrelor based on weight.

Smoking
Habitual smoking increased population mean clearance of ticagrelor by approximately 22% when compared to non-smokers. No dose adjustment is necessary for ticagrelor based on smoking status.

Effects of Other Drugs on BRILINTA
CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. The effects of other drugs on the pharmacokinetics of ticagrelor are presented in Figure 5 as change relative to ticagrelor given alone (test/reference). Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, and clarithromycin) substantially increase ticagrelor exposure. Moderate CYP3A inhibitors have lesser effects (e.g., diltiazem). CYP3A inducers (e.g., rifampin) substantially reduce ticagrelor blood levels.

Figure 5 – Effect of co-administered drugs on the pharmacokinetics of ticagrelor

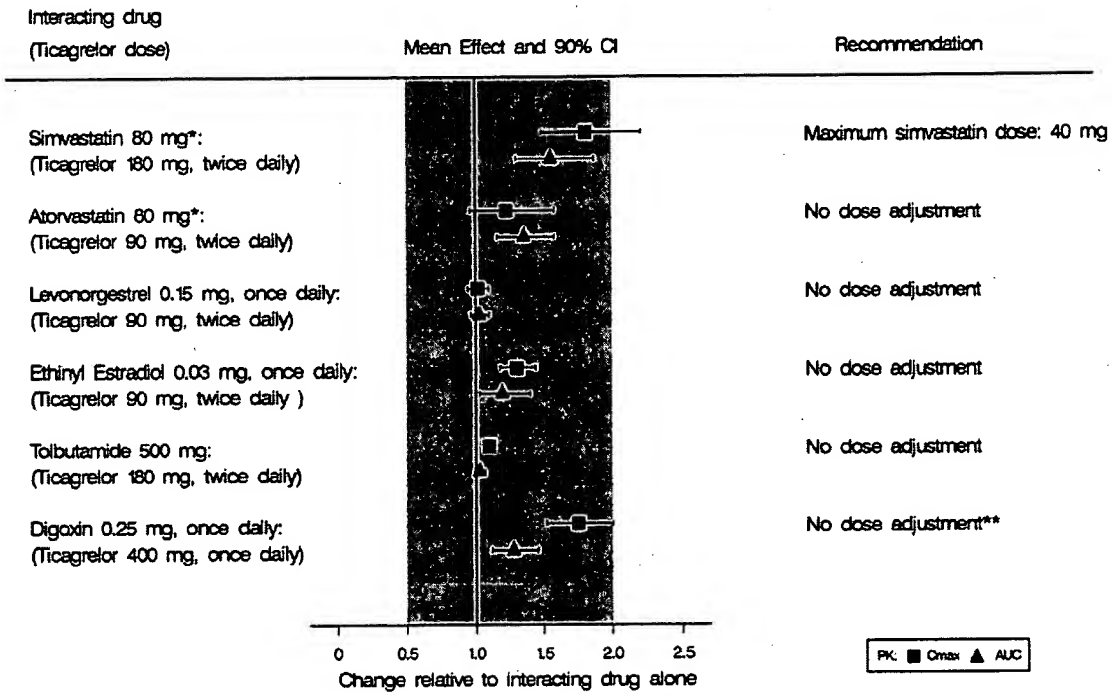


*See *Dosage and Administration (2)*.

Effects of BRILINTA on Other Drugs
In vitro metabolism studies demonstrate that ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5 and inhibitors of the

P-gp transporter. Ticagrelor and AR-C124910XX were shown to have no inhibitory effect on human CYP1A2, CYP2C19, and CYP2E1 activity. For specific *in vivo* effects on the pharmacokinetics of simvastatin, atorvastatin, ethinyl estradiol, levonorgesterol, tolbutamide, and digoxin, see Figure 6.

Figure 6 – Impact of BRILINTA on the pharmacokinetics of co-administered drugs



*Similar increases in AUC and C_{max} were observed for all metabolites
**Monitor digoxin levels with initiation of or change in BRILINTA therapy

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Ticagrelor was not carcinogenic in the mouse at doses up to 250 mg/kg/day or in the male rat at doses up to 120 mg/kg/day (19 and 15 times the MRHD of 90 mg twice daily on the basis of AUC, respectively). Uterine carcinomas, uterine adenocarcinomas and hepatocellular adenomas were seen in female rats at doses of 180 mg/kg/day (29-fold the maximally recommended dose of 90 mg twice daily on the basis of AUC), whereas 60 mg/kg/day (8-fold the MRHD based on AUC) was not carcinogenic in female rats.

Mutagenesis

Ticagrelor did not demonstrate genotoxicity when tested in the Ames bacterial mutagenicity test, mouse lymphoma assay and the rat micronucleus test. The active O-demethylated metabolite did not demonstrate genotoxicity in the Ames assay and mouse lymphoma assay.

Impairment of Fertility

Ticagrelor had no effect on male fertility at doses up to 180 mg/kg/day or on female fertility at doses up to 200 mg/kg/day (>15-fold the MRHD on the basis of AUC). Doses of ≥10 mg/kg/day given to female rats caused an increased incidence of irregular duration estrus cycles (1.5-fold the MRHD based on AUC).

14 CLINICAL STUDIES

The clinical evidence for the effectiveness of BRILINTA is derived from PLATO, a randomized double-blind study comparing BRILINTA (N=9333) to clopidogrel (N=9291), both given in combination with aspirin and other standard therapy, in patients with acute coronary syndromes (ACS). Patients were treated for at least 6 months and for up to 12 months. Study endpoints were obtained until the study was complete, even if drug was discontinued.

Patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms were randomized to receive BRILINTA or clopidogrel. Patients who had already been treated with clopidogrel could be enrolled and randomized to either study treatment. Patients could be included whether there was intent to manage the ACS medically or invasively, but patient randomization was not stratified by this intent. Subjects in the clopidogrel arm were treated with an initial loading dose of clopidogrel 300 mg, if previous clopidogrel therapy had not been given prior to randomization. Patients undergoing PCI could receive an additional 300 mg of clopidogrel at investigator discretion. All subjects randomized to BRILINTA received a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily. Concomitant aspirin was recommended at a loading dose of 160-500 mg. A daily maintenance dose of aspirin 75-100 mg was recommended, but higher maintenance doses of aspirin were allowed according to local judgment.

Because of ticagrelor's metabolism by CYP3A enzymes, the protocol recommended limiting the maximum dosage of simvastatin and lovastatin to 40 mg in both study arms. Because of an increased bleeding risk, the study excluded patients with previous intracranial hemorrhage, a gastrointestinal bleed within the past 6 months, or other factors that predispose to bleeding.

PLATO patients were predominantly male (72%) and Caucasian (92%). About 43% of patients were >65 years and 15% were >75 years.

The study's primary endpoint was the composite of first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or non-fatal stroke. The components were assessed as secondary endpoints.

Median exposure to study drug was 277 days. About half of the patients received pre-study clopidogrel and about 99% of the patients received aspirin at some time during PLATO. About 35% of patients were receiving a statin at baseline and 93% received a statin sometime during PLATO.

Table 4 shows the study results for the primary composite endpoint and the contribution of each component to the primary endpoint. Separate secondary endpoint analyses are shown for the overall occurrence of CV death, MI, and stroke and overall mortality.

Table 4 – Patients with Outcome Events, in PLATO (KM%)

	BRILINTA N=9333	Clopidogrel N=9291	Hazard Ratio (95% CI)	p-value
Composite of CV death, MI, or stroke	9.8	11.7	0.84 (0.77, 0.92)	0.0003
CV death	2.9	4.0	0.74	
Non-fatal MI	5.8	6.9	0.84	
Non-fatal stroke	1.4	1.1	1.24	
Secondary endpoints [a]				
CV death	4.0	5.1	0.79 (0.69, 0.91)	0.0013
MI[b]	5.8	6.9	0.84 (0.75, 0.95)	0.0045
Stroke[b]	1.5	1.3	1.17 (0.91, 1.52)	0.22
All-cause mortality	4.5	5.9	0.78 (0.69, 0.89)	0.0003

[a] First occurrence of specified event at any time

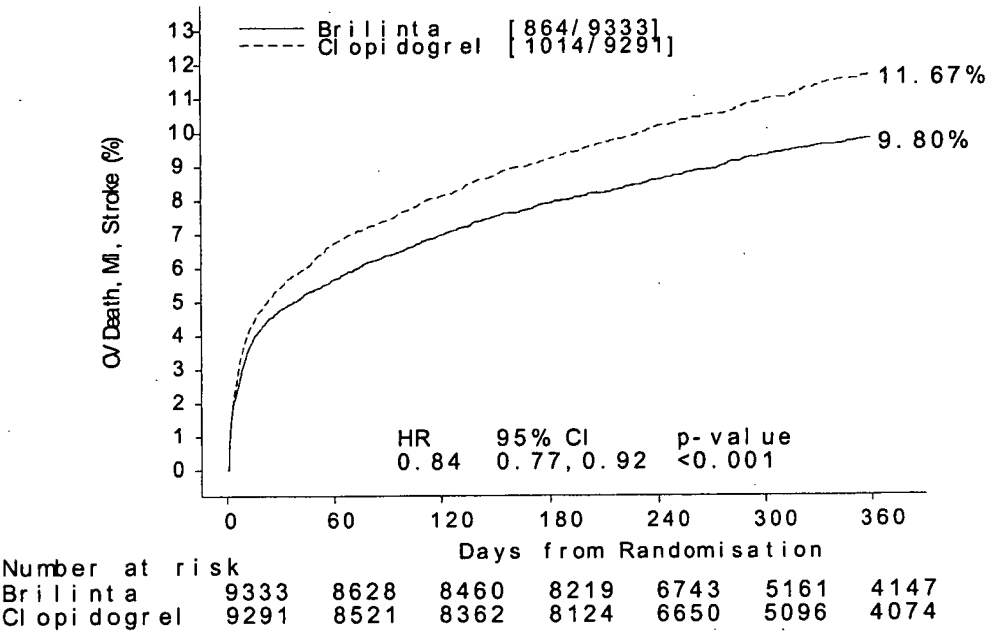
[b] Includes patients that could have had other non-fatal events or died

The difference between treatments on the composite resulted from effects on CV death and MI; each was statistically significant when considered as a secondary endpoint and there was no beneficial effect on strokes. For all-cause mortality the benefit was also statistically significant (p = 0.0003) with a hazard ratio of 0.78.

Among 11289 patients with PCI receiving any stent during PLATO, there was a lower risk of stent thrombosis (1.3% for adjudicated "definite") than with clopidogrel (1.9%) (HR 0.67, 95% CI 0.50-0.91; p=0.0091). The results were similar for drug-eluting and bare metal stents.

The Kaplan-Meier curve (Figure 7) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke in the overall study.

Figure 7 – Time to First Occurrence of CV death, MI, or Stroke in PLATO

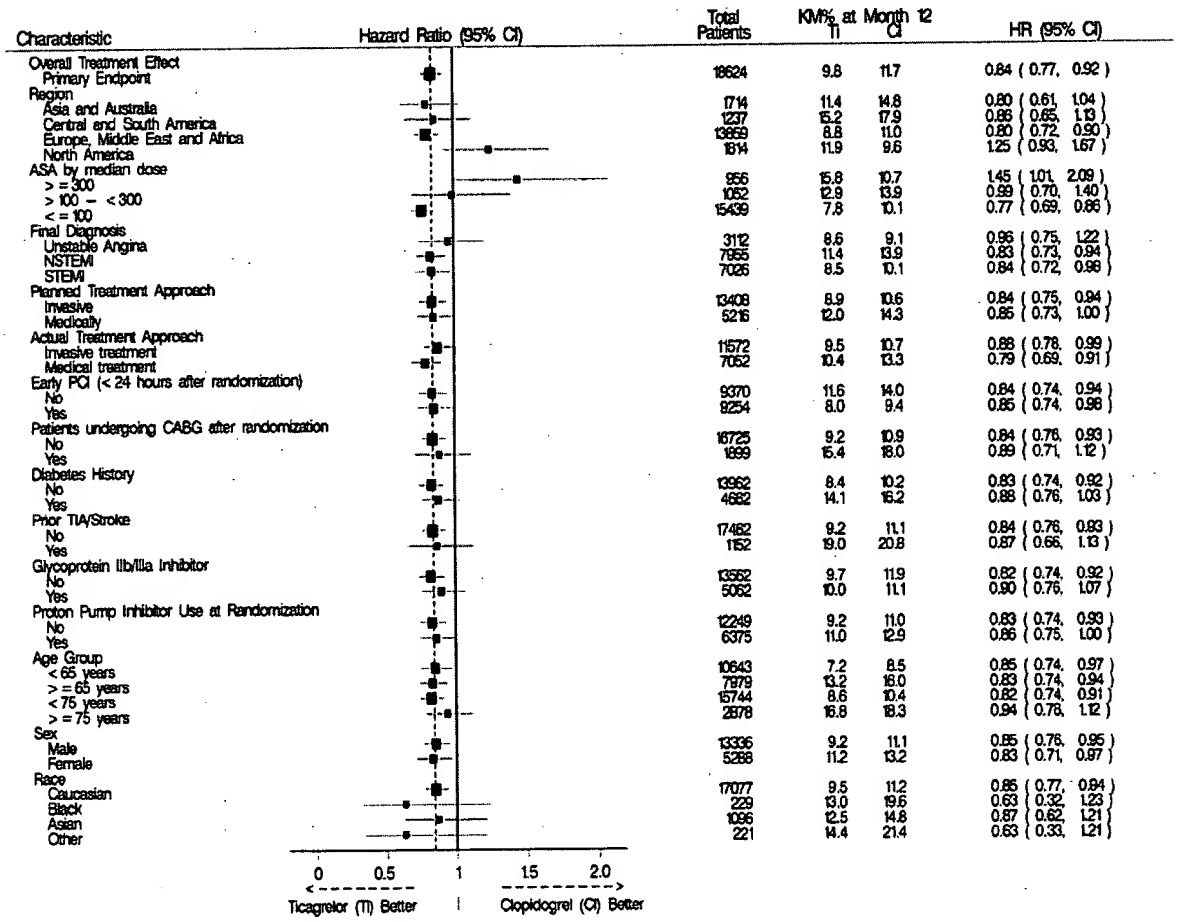


The curves separate by 30 days (RRR 12%) and continue to diverge throughout the 12 month treatment period (RRR 16%).

A wide range of demographic, concurrent baseline medications, and other treatment differences were examined for their influence on outcome. Many of these are shown in Figure 8. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. Most of the analyses show effects consistent with the overall results, but there are two marked exceptions: a finding of heterogeneity by region and a strong influence of the maintenance dose of aspirin. These are considered further below.

Most of the characteristics shown are baseline characteristics, but some reflect post-randomization determinations (e.g., final diagnosis, aspirin maintenance dose, use of PCI). Patients were not stratified by initial diagnosis, but the effect in the unstable angina subset (determined after randomization) appeared smaller than the effect in the NSTEMI and STEMI subsets. The results in the subsets based on final diagnosis (STEMI, NSTEMI and unstable angina) are also presented in Figure 8.

Figure 8 – Subgroup analyses of PLATO



Regional Differences

Results in the rest of the world compared to effects in North America (US and Canada) show a smaller effect in North America, numerically inferior to the control and driven by the US subset. The statistical test for the US/non-US comparison is statistically significant (p=0.009), and the same trend is present for both CV death and non-fatal MI. The individual results and nominal p-values, like all subset analyses, need cautious interpretation, and they could represent chance findings. The consistency of the differences in both the CV mortality and non-fatal MI components, however, supports the possibility that the finding is reliable.

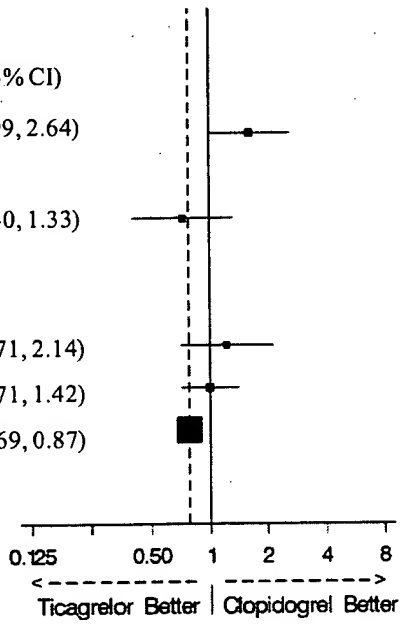
A wide variety of baseline and procedural differences between the US and non-US (including intended invasive vs. planned medical management, use of GPIIb/IIIa inhibitors, use of drug eluting vs. bare-metal stents) were examined to see if they could account for regional differences, but with one exception, aspirin maintenance dose, these differences did not appear to lead to differences in outcome.

Aspirin Dose

The PLATO protocol left the choice of aspirin maintenance dose up to the investigator and use patterns were very different in the US and elsewhere, with about 8% of non-US investigators using aspirin doses above 100 mg, and about 2% using doses above 300 mg, in contrast with US practice, where 57% of patients received doses above 100 mg and 54% received doses above 300 mg. Overall results favored BRILINTA when used with low maintenance doses (≤ 100 mg) of aspirin, and results analyzed by aspirin dose were similar in the US and elsewhere. Figure 8 shows overall results by median aspirin dose. Table 5 shows results by region and dose.

Table 5 – PLATO: CV Death, MI, Stroke by maintenance aspirin dose in the US and outside the US

		Ticagrelor		Clopidogrel		
Region	ASA Dose (mg)	N	Events	N	Events	HR (95% CI)
US	>=300	324	40	352	27	1.62 (0.99, 2.64)
	>100-<300	22	2	16	2	-
	<=100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	>=300	140	28	140	23	1.23 (0.71, 2.14)
	>100-<300	503	62	511	63	1.00 (0.71, 1.42)
	<=100	7449	546	7443	699	0.78 (0.69, 0.87)



Like any unplanned subset analysis, especially one where the characteristic is not a true baseline characteristic (but may be determined by usual investigator practice), the above analyses must be treated with caution. It is notable, however, that aspirin dose predicts outcome in both regions with a similar pattern, and that the pattern is similar for the two major components of the primary endpoint, CV death and non-fatal MI.

Despite the need to treat such results cautiously, there appears to be good reason to restrict aspirin maintenance dosage accompanying ticagrelor to 100 mg. Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of BRILINTA.

Pharmacogenetics
In a genetic substudy of PLATO (n=10,285), the effects of BRILINTA compared to clopidogrel on thrombotic events and bleeding were not significantly affected by CYP2C19 genotype.

16 HOW SUPPLIED/STORAGE AND HANDLING

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a "90" above "T" on one side.

Bottles of 60 – NDC 0186-0777-60
Bottles of 180 – NDC 0186-0777-18
100 count Hospital Unit Dose – NDC 0186-0777-39

Storage and Handling
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°- 86°F) [see USP controlled room temperature].

Keep BRILINTA in the container it comes in.

Keep BRILINTA tablets dry.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 Benefits and Risks

- Tell patients to take BRILINTA exactly as prescribed.
- Inform patients not to discontinue BRILINTA without discussing it with the prescribing physician.
- Tell patients daily doses of aspirin should not exceed 100 mg and to avoid taking any other medications that contain aspirin.
- Tell patients to read the Medication Guide.

17.2 Bleeding

Inform patients that they:

- Will bleed and bruise more easily
- Will take longer than usual to stop bleeding
- Should report any unanticipated, prolonged or excessive bleeding, or blood in their stool or urine.

17.3 Other Signs and Symptoms Requiring Medical Attention

- Inform patients that BRILINTA can cause shortness of breath. Tell them to contact their doctor if they experience unexpected shortness of breath, especially if severe.

17.4 Invasive Procedures

Instruct patients to:

- Inform physicians and dentists that they are taking BRILINTA before any surgery or dental procedure.
- Tell the doctor performing any surgery or dental procedure to talk to the prescribing physician before stopping BRILINTA.

17.5 Concomitant Medications

Tell patients to list all prescription medications, over-the-counter medications or dietary supplements they are taking or plan to take so the physician knows about other treatments that may affect bleeding risk (e.g. warfarin, heparin).

Issued: July 20, 2011

Manufactured by: AstraZeneca, AB S-151 85 Södertälje Sweden
Marketed by: AstraZeneca LP, Wilmington, DE 19850

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022433

NDA APPROVAL

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

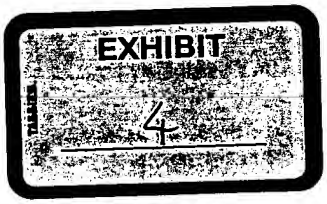
Please refer to your New Drug Application (NDA) dated November 13, 2009, received November 16, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brilinta (ticagrelor) 90 mg tablets.

We acknowledge receipt of your submissions received November 20, 24, 25 and December 8, 16, 18 (2), 22 and 24, 2009, and February 12, 16 (2), 26, March 5, 10, 15, 16, 18, April 8, 9, 26, 27, 30, May 3, 7, 12, 24, 28, June 3, 4 (2), 10 (2), 11 (2), 17, 18, 21, 22, 25, 30, July 16 (2), 20 (2), 23, 27 (2), 29, 30, August 4, 10, 11, 13, 18, 19 (2), 20 (2), 24, September 1, 8, October 1 and December 21, 2010, and January 20, 24, February 18 (3), 23 (2), March 7, 8, 11, 16, 21, 23, 28, 31, April 1, 8, 15 (2), 19, May 2, 4, 5, 23, June 2, 3 and July 6, 13 (2) and 14 (2), 2011.

The January 20, 2011 submission constituted a complete response to our December 16, 2010, action letter.

This new drug application provides for the use of Brilinta (ticagrelor) 90 mg tablets to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). Brilinta has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.

Brilinta has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of Brilinta. Avoid maintenance doses of aspirin above 100 mg daily.



We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022433.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. There are too few children with this disease/condition to study.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Brilinta (ticagrelor) to ensure the benefits of the drug outweigh the risks of bleeding and loss of efficacy when co-administered with maintenance doses of aspirin $\geq$ 100 mg daily.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Brilinta (ticagrelor) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Brilinta (ticagrelor). FDA has determined that Brilinta (ticagrelor) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Brilinta (ticagrelor) and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Brilinta (ticagrelor).

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on July 13, 2011, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Brilinta (ticagrelor) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. An evaluation of patients' understanding of the serious risks of Brilinta (ticagrelor).

2. An evaluation of healthcare providers' understanding of the serious risks of Brilinta (ticagrelor).

3. Number of Dear Healthcare Professional letters electronically sent, received, undeliverable, and opened.

4. Number of Dear Healthcare Professional letters sent via mail and number distributed by sales representatives.

5. Information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post-approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post-approval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If you plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022433 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022433
PROPOSED REMS MODIFICATION

REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022433
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
07/20/2011

US006525060B1

(12) **United States Patent**
Hardern et al.

(10) **Patent No.: US 6,525,060 B1**
(45) **Date of Patent: Feb. 25, 2003**

(54) **TRIAZOLO(4,5-D)PYRIMIDINE COMPOUNDS**

(75) Inventors: **David Hardern**, Sutton Bonington (GB); **Anthony Ingall**, Loughborough (GB); **Brian Springthorpe**, Loughborough (GB); **Paul Willis**, West Bridgford (GB); **Simon Guile**, Loughborough (GB)

(73) Assignee: **Astrazeneca UK Limited**, London (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/508,195**

(22) PCT Filed: **Dec. 2, 1999**

(86) PCT No.: **PCT/SE99/02256**

§ 371 (c)(1),
(2), (4) Date: **Mar. 8, 2000**

(87) PCT Pub. No.: **WO00/34283**

PCT Pub. Date: **Jun. 15, 2000**

(30) **Foreign Application Priority Data**

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Apr. 9, 1999 (SE) 9901271

(51) **Int. Cl.**[7] **A61K 31/519**; C07D 487/04
(52) **U.S. Cl.** **514/258**; 544/254
(58) **Field of Search** 514/258; 544/254

(56) **References Cited**

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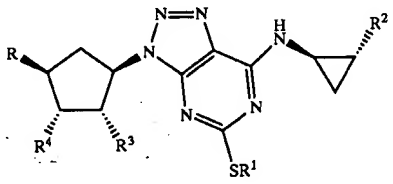
Primary Examiner—John M. Ford

(57) **ABSTRACT**

Triazolo[4,5-d]pyrimidine compounds, their use as medicaments, compositions containing them and processes for their preparation. The compounds of the invention have the formula (I) as follows:

(I)



wherein R, X and R^1 through R^3 are as defined in the specification.

14 Claims, No Drawings

TRIAZOLO(4,5-D)PYRIMIDINE COMPOUNDS

This is a 371 National Phase application of PCT/SE99/02256, filed Dec. 2, 1999.

FIELD OF THE INVENTION

The present invention provides new triazolo[4,5-d] pyrimidine compounds, their use as medicaments, compositions containing them and processes for their preparation.

BACKGROUND OF THE INVENTION

Platelet adhesion and aggregation are initiating events in arterial thrombosis. Although the process of platelet adhesion to the sub-endothelial surface may have an important role to play in the repair of damaged vessel walls, the platelet aggregation that this initiates can precipitate acute thrombotic occlusion of vital vascular beds, leading to events with high morbidity such as myocardial infarction and unstable angina. The success of interventions used to prevent or alleviate these conditions, such as thrombolysis and angioplasty is also compromised by platelet mediated occlusion or re-occlusion.

A number of converging pathways lead to platelet aggregation. Whatever the initial stimulus, the final common event is a cross-linking of platelets by binding of fibrinogen to a membrane-binding site, glycoprotein IIb/IIIa (GPIIb/IIIa). The high anti-platelet efficacy of antibodies or antagonists for GPIIb/IIIa is explained by their interference with this final common event. However, this efficacy may also explain the bleeding problems that have been observed with this class of agent. Thrombin can produce platelet aggregation largely independently of other pathways but substantial quantities of thrombin are unlikely to be present without prior activation of platelets by other mechanisms. Thrombin inhibitors such as hirudin are highly effective antithrombotic agents, but again may produce excessive bleeding because they function as both anti-platelet and anticoagulant agents (The TIMI 9a Investigators (1994), *Circulation* 90, pp. 1624–1630; The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIIa Investigators (1994) *Circulation* 90, pp. 1631–1637; Neuhaus K. L. et. al. (1994) *Circulation* 90, pp. 1638–1642).

It has been found that adenosine 5'-diphosphate (ADP) acts as a key mediator of thrombosis. A pivotal role for ADP is supported by the fact that other agents, such as adrenaline and 5-hydroxytryptamine (5HT, serotonin) will only produce aggregation in the presence of ADP. The limited anti-thrombotic efficacy of aspirin may reflect the fact that it blocks only one source of ADP which is that released in a thromboxane-dependent manner following platelet adhesion (see e.g. Antiplatelet Trialists' Collaboration (1994), *Br. Med. J.* 308, pp. 81–106 and Antiplatelet Trialists' Collaboration (1994), *Br. Med. J.* 308, pp. 159–168). Aspirin has no effect on aggregation produced by other sources of ADP, such as damaged cells or ADP released under conditions of turbulent blood flow.

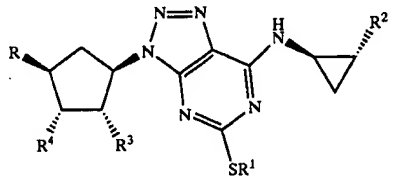
ADP-induced platelet aggregation is mediated by the P_{2T} receptor subtype located on the platelet membrane. The P_{2T} receptor (also known as $P2Y_{ADP}$ or $P2T_{AC}$) is primarily involved in mediating platelet aggregation/activation and is a G-protein coupled receptor which is as yet uncloned. The pharmacological characteristics of this receptor have been described, for example, in the references by Humphries et al., *Br. J. Pharmacology* (1994), 113, 1057–1063, and Fagura et al., *Br. J. Pharmacology* (1998) 124, 157–164.

Recently it has been shown that antagonists at this receptor offer significant improvements over other anti-thrombotic agents (see *J. Med. Chem.* (1999) 42, 213). Accordingly there is a need to find further P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) antagonists as anti-thrombotic agents.

International Patent Application WO 9905143 discloses generically a series of triazolo[4,5-d]pyrimidine compounds having activity as P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) antagonists. It has now been found that certain compounds within the scope of International Patent Application WO 9905143 but not specifically disclosed therein exhibit high potency combined with surprisingly high metabolic stability and bioavailibility, such that the predicted therapeutic dose for prolonged inhibition of aggregation in man shows advantage.

DESCRIPTION OF THE INVENTION

In a first aspect the invention therefore provides a compound of formula (I):



(I)

wherein:

R^1 is C_{3-5} alkyl optionally substituted by one or more halogen atoms;

R^2 is a phenyl group, optionally substituted by one or more fluorine atoms;

R^3 and R^4 are both hydroxy;

R is XOH, where X is CH_2, OCH_2CH_2 or a bond;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

provided that:

when X is CH_2 or a bond, R^1 is not propyl.

when X is CH_2 and R^1 is $CH_2CH_2CF_3$, butyl or pentyl, the phenyl group at R^2 must be substituted by fluorine.

when X is OCH_2CH_2 and R^1 is propyl, the phenyl group at R^2 must be substituted by fluorine.

Alkyl groups, whether alone or as part of another group are straight chained and fully saturated.

Suitably R^1 is a C_{3-5} alkyl optionally substituted by one or more fluorine atoms. Preferably R^1 is C_{3-5} alkyl optionally substituted on the terminal carbon by three fluorine atoms. More preferably R^1 is 3,3,3,-trifluoropropyl, butyl or propyl.

Suitably R^2 is phenyl or phenyl substituted by one or more fluorine atoms. Preferably R^2 is phenyl, 4-fluorophenyl or 3,4-difluorophenyl.

Suitably R is XOH where X is CH_2, OCH_2CH_2 or a bond. Preferably R is CH_2OH or OCH_2CH_2OH.

Particularly preferred compounds include:

[1R-[1α,2α,3β(1R*,2S*),5β]]-3-[7-[[2-(4-Fluorophenyl) cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1, 2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol;

[1R-[1α,2α,3β(1R*,2S*),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol;

[1S-(1α,2α,3β(1S*,2R*),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-

1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol;

[1R-[1α,2α,3β(1R*,2S*),5β]]-3-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol;

[1S-[1α,2β,3β,4α(1S*,2R*)]]-4-[5-(Butylthio)-7-[[2-(4-fluorophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-cyclopentane-1,2,3-triol;

[1S-(1α,2α,3β(1S*,2R*),5β)]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol;

[1S-[1α,2α,3β,5β(1S*,2R*)]]-3-(2-Hydroxyethoxy)-5-[7-(2-phenylcyclopropyl)amino]-5-[(3,3,3-trifluoropropyl) thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-cyclopentane-1,2-diol [1S-[1α,2β,3β,4α(1S*, 2R*)]]-4-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl] amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl] cyclopentane-1,2,3-triol;

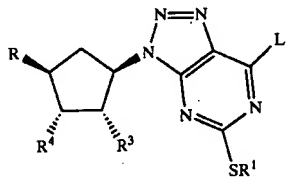
[1S-[1α,2α,3β(1S*,2R*),5β]]-3-[5-(Butylthio)-7-[(2-phenylcyclopropyl)amino]-3H-1,2,3-triazolo[4,5-d] pyrimidin-3-yl]-5-(2-hydroxethoxy)-cyclopentane-1,2-diol;

and pharmaceutically acceptable salts or solvates thereof, or solvates of such salts.

According to the invention there is further provided a process for the preparation of a compound of formula (I) which comprises:

(a) reacting a compound of formula (II):

(II)



where R, R^1, R^3 and R^4 are as defined in formula (I), or are protected derivatives thereof, or R^3 and R^4 together form a bond in the 5-membered ring, or R is CH_2CH_2OR', where R is C_{1-6} alkyl or benzyl, and L is a leaving group such as halogen or SR, with a compound of formula (III):

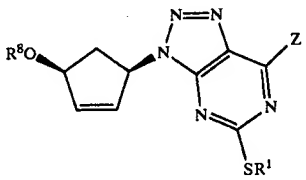
(III)

where R^2 is as defined in formula (I), or is a protected derivative thereof,

or where X is a bond:

(b) hydroxylation of a compound of formula (IV):

(IV)



where R^1 is defined in formula (I) and R^8 is H or $CH_2CH_2OP^3$ where P^3 is H or a protecting group or R^8 is CH_2COOR' where R' is C_{1-6} alkyl or benzyl, and Z is NH_2 or

where R^2 is defined in formula (I).

and for both (a) and (b) optionally thereafter and in any order:

converting one or more functional groups into further functional groups;

removing any protecting groups;

forming a pharmaceutically acceptable salt or solvate, or a solvate of such a salt.

Compounds of formula (II) can be reacted with amines of formula (III) in the presence of a base, such as a tertiary organic amine, in an inert solvent, such as dichloromethane, at ambient or elevated temperature. Other suitable bases include inorganic bases such as potassium carbonate.

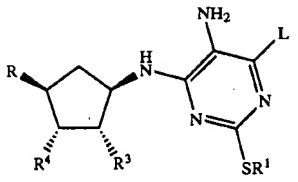
The hydroxy groups R^3 and R^4 can be protected as groups OP^1 and OP^2 where P^1 and P^2 are protecting groups. Examples of suitable protecting groups in compounds of formula (II) are C_{1-6} alkyl (preferably methyl), benzyl, $(C_{1-6}alkyl)_3Si$ (preferably t-butyldimethylsilyl), and a C(O) C_{1-6}alkyl group such as acetyl. Preferably the two groups P^1 and P^2 together with the atoms to which they are attached form an alkylidene ring such as a methylidene or isopropylidene ring. Alternatively P^1 and P^2 can form an alkoxymethylidene ring such as ethoxymethylidene.

Protecting groups can be added and removed using known reaction conditions. The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

Ester protecting groups can be removed by basic hydrolysis, for example by using a metal hydroxide, preferably an alkali metal hydroxide, such as sodium hydroxide or lithium hydroxide, or quaternary ammonium hydroxide in a solvent, such as aqueous ethanol or aqueous tetrahydrofuran, at a temperature of from 10° to 100° C., preferably the temperature is around room temperature; or by acidic hydrolysis using a mineral acid such as HCl or a strong organic acid such as trichloroacetic acid in a solvent such as aqueous 1,4-dioxane. Trialkylsilyl protecting groups can be removed by the use of, for example, a fluoride ion source, for example tetra-n-butylammonium fluoride or hydrogen fluoride. When one or both of P^1 and are C_{1-6} alkyl, deprotection can be achieved using boron tribromide. Benzyl groups can be removed by hydrogenolysis using a transition metal catalyst, for example palladium on charcoal, under an atmosphere of hydrogen, at a pressure of from 1 to 5 bar, in a solvent, such as acetic acid.

A compound of formula (II) can be prepared by diazotising a compound of formula (V):

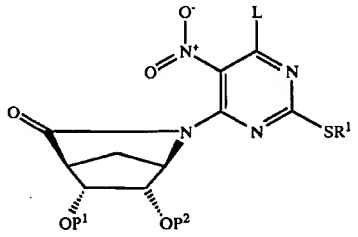
(V)



wherein R^1 is as defined in formula (I), and R is as defined in formula (I), or is a protected derivative thereof, or is OCH_2CO_2R', where R' is C_{1-6} alkyl or benzyl, and L is as defined above and R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof or R^3 and R^4 together form a bond in the 5-membered ring, with a metal nitrite, for example an alkali metal nitrite, especially sodium nitrite in dilute aqueous acid, for example 2M HCl, or with a C_{1-6}-alkyl nitrite, in an inert solvent, at a temperature of from about −20 to about 100° C. Preferred conditions are isoamyl nitrite in acetonitrile at about 80° C.

A compound of formula (V) wherein R is CH_2OH, R^3 and R^4 are hydroxyl or protected derivatives thereof and L is as defined above, can be prepared by reducing a compound of formula (VI):

(VI)



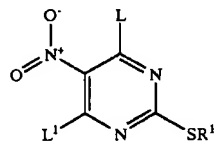
wherein R^1, L, P^1 and P^2 are as defined above.

The reduction of the nitro group can be carried out for example by using hydrogenation with a transition metal catalyst at a temperature around room temperature, for example palladium on charcoal under an atmosphere of hydrogen, preferably at a pressure from 1 to 5 atmospheres, in a solvent, for example ethanol, or by using iron in an acidic solvent such as acetic acid at a temperature of about 100° C.

Reduction of the lactam can be carried out using complex metal hydrides such as lithium aluminium hydride in a solvent such as ether or preferably, by using sodium borohydride in a suitable solvent such as methanol.

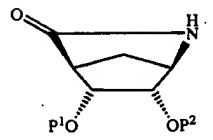
A compound of formula (VI) can be prepared by reacting a compound of formula (VII):

(VII)



wherein L and R^1 are as defined above and L^1 is a leaving group, for example a halogen atom, wherein L and L^1 are preferably the same, with a compound of formula (VIII):

(VIII)



wherein P^1 and P^2 are as defined above, in the presence of a base such as C_{1-6}-alkyl-M or MH wherein M is a metal ion, for example n-butyl lithium, in an inert solvent, such as tetrahydrofuran, at a temperature of from about −10 to about 100° C. Preferably sodium hydride is used in tetrahydrofuran at room temperature.

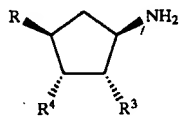
One or more functional groups can be converted into further functional groups using standard chemistry. A compound where X is a bond can be converted to a compound where X is $O(CH_2)_2$ by treatment with base followed by LY where L is a leaving group and Y is $(CH_2)_2OH$ or a protected version thereof or Y is CH_2COOR' where R' is C_{1-6} alkyl or benzyl. A compound where R is CH_2CH_2OR may be converted into a compound where R is $O(CH_2)_2OH$ by reduction, for example using DIBAL-H®. The group SR^1 can be interconverted by oxidation of the sulfur, for example using oxone™ or mCBPA, followed by treatment with a compound $R^{1'}$-SM where $R^{1'}$ is a different R^1 group and M is a metal such as sodium. Alternatively the product of the sulfur oxidation may be treated with MSH where M is a metal such as sodium, followed by treatment with a base and $R^{1'}X$ where $R^{1'}$ is a different R^1 group and X is a leaving group. Suitable bases include N,N-diisopropylethylamine.

A compound of formula (II) where R, R^1, R^3, and R^4 are as defined in formula (I) or are protected derivatives thereof, or R^3 and R^4 together form a bond in the 5-membered ring, or R is OCH_2CO_2R' where R' is C_{1-6} alkyl or benzyl, and L is a leaving group such as halogen, may be converted into a compound of formula (II) where R, R^1, R^3, and R^4 are defined above and L is NH_2 by treatment with a diazotizing agent in the presence of a halogenating agent, preferably isoamyl-nitrite and carbon tetrabromide.

A compound of formula (II) where R, R^1, R^3, and R^4 are defined above and L is NH_2 may be prepared by treating a compound of formula (II) where R, R^1, R^3, and R^4 are as defined above and L is a leaving group such as halogen, with ammonia in a solvent such as methanol.

Compounds of formula (V) can also be prepared by treating a compound of formula (XI)

(XI)



where R, R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof or R is OCH_2CO_2R' where R' is C_{1-6} alkyl or benzyl, or R^3 and R^4 together form a bond in the 5-membered ring,

with a compound of formula (VII) as defined above, followed by reduction of the nitro group. The reaction is carried out in an inert solvent such as dichloromethane or 1,4-dioxane, in the presence of a non-nucleophilic base, such as N,N-diisopropylamine, at a tempeature of about −20° C. to about 150° C., preferably at ambient temperature.

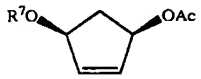
Compounds of formula (II) where R is as defined in formula (I), R^3 and R^4 together form a bond in the

5-membered ring, and L is SR^1, or a protected derivative thereof, can be prepared by reacting a compound of formula (XII):

(XII)

where R^1 groups are as defined in formula (I), with a compound of formula (XIII):

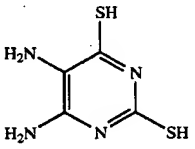
(XIII)



in which R^7 is H or a protected derivative thereof. The reaction can be carried out in the presence of a suitable transition metal complex, preferably tetrakistriphenylphosphine palladium(0).

Compounds of formula (XII) can be prepared from compounds of formula (XIV):

(XIV)



by reacting with a compound R^1X where R^1 is as defined in formula (I) and X is a leaving group such as halo, followed by cyclisation.

Compounds of formula (XI) where R is OH or a protected version thereof and R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof may be prepared from compounds of formula (XIII) where R^7 is H or a protecting group by treatment with a bisester of imidodicarbamic acid using palladium catalysis followed by hydroxylation of the double bond, and optionally, deprotection of the nitrogen. Preferably imidodicarbonic acid, bis-(1,1-dimethylethyl) ester and tetrakistriphenylphosphine palladium(0) are used followed by osmium tetroxide and deprotection using hydrochloric acid in methanol.

Compounds of formula (XI), where R is OCH_2CO_2R' where R' is C_{1-6} alkyl and R^3 and R^4 together form a bond in the 5-membered ring, may be formed from compounds of formula (XIII), where R^7 is H or a protecting group, by treatment with an azide in the presence of a palladium catalyst, followed by reduction of the azide and alkylation of the alcohol as described previously.

Compounds of formula (XI) where R is OCH_2CH_2OH and R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof may be prepared from compounds of formula (XI) where R is OH and R^3 and R^4 are as defined in formula (I) or are protected derivatives thereof, by protection of the nitrogen, alkylation of the alcohol using a 2-halo-acetic acid ester, followed by reduction of the ester and deprotection of the nitrogen. We prefer protection of the nitrogen as a carbobenzyloxy derivative using benzyl chloroformate followed by alkylation of the alcohol using ethyl bromoacetate and potassium t-butoxide, reduction of the ester using lithium borohydride in tetrahydrofuran and deprotection of the nitrogen by hydrogenation in the presence of palladium on carbon. In addition we prefer the case where the alcohols R^3 and R^4 are protected as an isopropylidene ring.

The amines of formula (III) can be prepared using procedures described in H Nishiyama et al, Bull. Chem. Soc., Jpn., 1995, 68, 1247, P. Newman, Optical Resolution Procedures for Chemical Compounds, Vol. 1, Amines and Related Compounds; Optical Resolution and Information Centre: Manhattan College, Riverdale, N.Y., 1978, p120, J. Vallgarda et al, J. Chem. Soc. Perkin 1, 1994, 461 or in International Patent Application WO 9905143.

All novel intermediates form a further aspect of the invention.

Salts of the compounds of formula (I) may be formed by reacting the free acid, or a salt thereof, or the free base, or a salt or a derivative thereof, with one or more equivalents of the appropriate base (for example ammonium hydroxide optionally substituted by C_{1-6}-alkyl or an alkali metal or alkaline earth metal hydroxide) or acid (for example a hydrohalic (especially HCl), sulphuric, oxalic or phosphoric acid). The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. water, ethanol, tetrahydrofuran or diethyl ether, which may be removed in vacuo, or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin. The non-toxic physiologically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

The compounds of the invention act as P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) receptor antagonists. Accordingly, the compounds are useful in therapy, including combination therapy, particularly they are indicated for use as: inhibitors of platelet activation, aggregation and degranulation, promoters of platelet disaggregation, anti-thrombotic agents or in the treatment or prophylaxis of unstable angina, primary arterial thrombotic complications of atherosclerosis such as thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease, myocardial infarction with or without thrombolysis, arterial complications due to interventions in atherosclerotic disease such as angioplasty, including coronary angioplasty (PTCA), endarterectomy, stent placement, coronary and other vascular graft surgery, thrombotic complications of surgical or mechanical damage such as tissue salvage following accidental or surgical trauma, reconstructive surgery including skin and muscle flaps, conditions with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, thrombotic complications of septicaemia, adult respiratory distress syndrome, anti-phospholipid syndrome, heparin-induced thrombocytopaenia and pre-eclampsia/eclampsia, or venous thrombosis such as deep vein thrombosis, venoocclusive disease, haematological conditions such as myeloproliferative disease, including thrombocythaemia, sickle cell disease; or in the prevention of mechanically-induced platelet activation in vivo, such as cardiopulmonary bypass and extracorporeal membrane oxygenation (prevention of microthromboembolism), mechanically-induced platelet activation in vitro, such as use in the preservation of blood products, e.g. platelet concentrates, or shunt occlusion such as in renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis, inflammatory bowel disease

and organ graft rejection, conditions such as migraine, Raynaud's phenomenon, conditions in which platelets can contribute to the underlying inflammatory disease process in the vascular wall such as atheromatous plaque formation/progression, stenosis/restenosis and in other inflammatory conditions such as asthma, in which platelets and platelet-derived factors are implicated in the immunological disease process. Further indications include treatment of CNS disorders and prevention of the growth and spread of tumours.

According to the invention there is further provided the use of a compound according to the invention as an active ingredient in the manufacture of a medicament for use in the treatment or prevention of the above disorders. In particular the compounds of the invention are useful for treating myocardial infarction, thrombotic stroke, transient ischaemic attacks, peripheral vascular disease and stable and unstable angina, especially unstable angina. The invention also provides a method of treatment or prevention of the above disorders which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of a compound according to the invention.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration in the form of sterile parenteral solutions or suspensions, by subcutaneous administration, or by rectal administration in the form of suppositories or transdermally.

The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant and/or carrier. Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

Dry powder formulations and pressurised HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided. The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers include sugars and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound with or without a carrier substance is delivered to the patient.

The pharmaceutical composition comprising the compound of the invention may conveniently be tablets, pills, capsules, syrups, powders or granules for oral administration; sterile parenteral or subcutaneous solutions, suspensions for parenteral administration or suppositories for rectal administration.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved either in a readily volatile organic solvent or an aqueous solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets, e.g. lactose, saccharose, sorbitol, mannitol, starches, cellulose derivatives or gelatine. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

EXAMPLES

The invention is illustrated by the following non-limiting examples.

In the examples the NMR spectra were measured on a Varian Unity Inova 300 or 400 spectrometer and the MS spectra were measured as follows: EI spectra were obtained on a VG 70-250S or Finnigan Mat Incos-XL spectrometer, FAB spectra were obtained on a VG70-250SEQ spectrometer, ESI and APCI spectra were obtained on Finnigan Mat SSQ7000 or a Micromass Platform spectrometer. Preparative HPLC separations were generally performed using a Novapak®, Bondapak® or Hypersil® column packed with BDSC-18 reverse phase silica. Flash chromatography (indicated in the Examples as (SiO_2)) was carried out using Fisher Matrix silica, 35–70 μm. For examples which showed the presence of rotamers in the proton NMR spectra only the chemical shifts of the major rotamer are quoted.

Example 1

[1R-[1α,2α,3β(1R*,2S*),5β]]-3-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol

a) [3aS-[1(E),3aα,6α,7aβ]]-1-[3-(4-Fluorophenyl)-1-oxo-2-propenyl]-hexahydro-8,8-dimethyl-3H-3a,6-methano-2,1-benzisothiazole-2,2-dioxide

A mixture of 3-(4-fluorophenyl)-2-propenoic acid (3.0 g) and thionyl chloride (5.0 ml) was stirred at 70° C. for 1 hour, the reaction mixture was then concentrated under reduced pressure. The residue was azeotroped twice with dichloromethane then dissolved in toluene (10 ml). To a suspension of sodium hydride (60% dispersion in oil; 0.99 g) in toluene (40 ml) was added a solution of [3aS-(3aα,6α,7aβ)]-hexahydro-8,8-dimethyl-3H-3a,6-methano-2,1-

benzisothiazole-2,2-dioxide (3.89 g) in toluene (40 ml) and the mixture stirred for 30 minutes. To the reaction mixture was then added the solution described above and the resulting suspension was stirred for 16 hours. Water (200 ml) was added, the organics collected and the aqueous extracted into dichloromethane (3×100 ml). The organics were combined, dried and concentrated. Recrystallisation (ethanol) gave the subtitle compound as colourless needles (5.92 g).

MS (APCI) 364 ($M+H^+$,100%)

b) [3aS-[1(1S*,2S*),3aα,6α,7aβ]]-1-[[2-(4-Fluorophenyl) cyclopropyl]carbonyl]-hexahydro-8,8-dimethyl-3H-3a,6-methano-2,1-benzisothiazole-2,2-dioxide

A solution of diazomethane (2.9 g) in ether (150 ml) (prepared as described in Vogel's Textbook of Practical Organic Chemistry, Fifth Edition, Longman Scientific and Technical, p432) was added to a solution of the product of step a) (5.90 g) and palladium(II) acetate (18 mg) in dichloromethane (350 ml) at 0° C. and the reaction mixture stirred at 0° C. for 5 hours. Acetic acid (5 ml) was added and the reaction mixture was then washed with saturated sodium bicarbonate solution (200 ml) and the organics filtered through a plug of silica. After concentrating in vacuo, the residue was recrystallised (ethanol) to give the subtitle compound as colourless needles (3.81 g).

MS (APCI) 378 ($M+H^+$,100%)

c) (1R-trans)-2-(4-Fluorophenyl)-cyclopropanecarboxylic acid

A suspension of the product from step b) (3.74 g) and lithium hydroxide monohydrate (4.11 g) in tetrahydrofuran (100 ml)/water (3 ml) was stirred at 50° C. for 24 hours. The reaction mixture was concentrated in vacuo, and the residue dissolved in water (100 ml), acidified with 2N HCl and extracted into dichloromethane (3×75 ml). The organics were dried and concentrated. Purification (SiO_2, isohexane:diethylether 2:1 as eluant) gave the subtitle compound as a colourless solid (1.78 g).

MS (APCI) 179 ($M-H^+$,100%)

d) (1R-trans)-2-(4-Fluorophenyl)cyclopropanamine, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1)

To a solution of the product from step c) (1.78 g) and triethylamine (2.7 ml) in acetone/water (10:1, 23 ml) at 0° C. was added ethyl chloroformate (2.0 ml) over 5 min. The solution was maintained at 0° C. for 30 minutes before addition of sodium azide (1.52 g) in water (6 ml). After a further hour, water (350 ml) was added and the reaction mixture extracted with toluene (3×100 ml). The organic extracts were combined and dried, then heated at reflux for 2 hours behind a blast screen. After cooling the solution, 6N HCl (50 ml) was added and the mixture heated at reflux for 3 hours. Water (150 ml) was added and the aqueous phase basified with 2N NaOH (aq), then extracted into dichloromethane (3×100 ml). The organic phase was dried and concentrated. The amine was dissolved in ethanol (5 ml) and a solution of L-tartaric acid (1.48 g) in ethanol (20 ml) was added. After 20 minutes the solid was collected affording the subtitle compound as colourless needles (1.12 g).

NMR δH (d_6-DMSO) 1.07–1.39 (1H, m), 1.22–1.29 (1H, m), 2.16–2.23 (1H, m), 2.64–2.70 (1H,m), 3.95 (2H, s), 7.06–7.19 (4H, m)

e) [3aR-[3aα,4α,6α(1R*,2S*),6aα]]-6-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol

N,N-Diisopropylethylamine (1.29 g) was added to a solution of [3aR-(3aα,4α,6α,6aα)]-6-[7-chloro-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol (prepared as described in International Patent Application WO 9703084) (1.0 g) and the product of step d) (0.75 g) in dichloromethane (25 ml). The reaction mixture was stirred at room temperature for 3 hours, then washed with water, dried and evaporated. The residue was purified (SiO_2, ethyl acetate:isohexane 1:1 as eluent) to afford the subtitle compound (1.25 g).

MS (APCI) 515 ($M+H^+$, 100%)

f) [3aR-[3aα,4α,6α(1R*,2S*),6aα]]-6-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-(propylsulphonyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol

3-Chloroperoxybenzoic acid (70%, 1.8 g) was added to a suspension of the product of step e) (1.25 g) in ethanol (25 ml) and the resulting solution stirred at room temperature for 2 hours. The reaction mixture was concentrated and the residue taken up in ethyl acetate (500 ml), washed with 10% aqueous sodium metabisulfite solution (2×100 ml) and 10% aqueous sodium bicarbonate solution (2×100 ml) then dried and concentrated to afford the subtitle compound (1.4 g).

MS (APCI) 547 ($M+H^+$, 100%)

g) [[3aR-[3aα,4α,6α(1R*,2S*),6aα]]-6-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropy)lthio]-3H-1,2,3-triazolo[4,5d]pyrimidin-3-yl)-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol

Sodium hydrosulfide hydrate (1.4 g) was added to a solution of the product of step f) (1.4 g) in dimethyl sulphoxide (20 ml) and the solution stirred at room temperature for 1.5 hours. Brine (150 ml) was added and the mixture acidified with acetic acid then extracted with ethyl acetate (3×100 ml). The organic phase was dried and concentrated and the residue azeotroped with toluene (3×100 ml). The residue was dissolved in N,N-dimethylformamide (20 ml) then N,N-diisopropylethylamine (0.33 g) and 3,3,3-trifluoropropylbromide (0.48 g) added. After stirring at 50° C. for 30 minutes the reaction mixture was diluted with ethyl acetate (100 ml) then washed with aqueous brine (3×100 ml), dried and concentrated then the residue purified (SiO_2, isohexane:ethyl acetate 1:1 as eluant) to afford the subtitle compound (1.4 g).

MS (APCI) 569 ($M+H^+$, 100%)

h) [1R-[1α,2α,3β(1R*,2S*),5β]]-3-[7-[[2-(4-Fluorophenyl) cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol

A solution of the product from step g) (1.4 g) in trifluoroacetic acid (10 ml) and water (2 ml) was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate (400 ml) then washed with sodium bicarbonate solution (400 ml), dried and evaporated. The residue was purified (SiO_2, methanol:chloroform 3:47 as eluant) to afford the title compound (0.44 g).

MS (APCI) 529 ($M+H^+$,100%)

NMR δH (d_6-DMSO) 9.42 (1H, d), 7.27–7.22 (2H, m), 7.14–7.08 (2H, m), 5.01–4.95 (2H, m), 4.73–4.70 (2H, m), 4.44–4.41 (1H, m), 3.87–3.84 (1H, m), 3.50–3.45 (2H, m), (3H, m), 2.60–2.55 (1H, m), 2.28–2.20 (2H, m), 2.10–2.06 (1H, m), 1.90–1.8 (1H, m), 1.49–1.46 (1H, m), 1.33–1.30 (1H, m).

Example 2

[1R-[1α,2α,3β(1R*,2S*),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d] pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1, 2-diol

a) [3aS-[1(E),3aα,6α,7aβ]]-1-[3-(3,4-Difluorophenyl)-1-oxo-2-propenyl]-hexahydro-8,8-dimethyl-3H-3a,6-methano-2,1-benzisothiazole-2,2-dioxide

The subtitle compound was prepared according to the method of Example 1, step a) using 3-(3,4-difluorophenyl)-2-propenoic acid.

MS (APCI) 382 ($M+H^+$, 100%)

b) [3aS-[1(1S*,2S*),3aα,6α,7aβ]]-1-[[2-(3,4-Difluorophenyl)cyclopropyl]carbonyl]-hexahydro-8,8-dimethyl-3H-3a,6-methano-2,1-benzisothiazole-2,2-dioxide

The subtitle compound was prepared according to the method of Example 1, step b) using the product of step a).

MS (APCI) 396 ($M+H^+$, 100%)

c)(1R-trans)-2-(3,4-Difluorophenyl)-cyclopropane carboxylic acid

The subtitle compound was prepared according to the method of Example 1, step c) using the product of step b).

NMR δH ($CDCl_3$) 7.06 (1H, dt, J=10.0, J=8.5 Hz), 6.93–6.80 (2H, m), 2.58–2.52 (1H, m), 1.88–1.82 (1H, m), 1.66 (1H,dt, J=9.2, J=5.2 Hz), 1.34 (1H, ddd, J=8.5, J=6.5, J=4.8 Hz).

d)(1R-trans)-2-(3,4-Difluorophenyl)cyclopropanamine, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1)

The subtitle compound was prepared according to the method of Example 1, step d) using the product of step c).

MS (APCI) 170 ($M+H^+$, 100%)

e)[3aR-[3aα,4α,6α(1R*,2S*),6aα]-6-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol

Isoamyl nitrite (5.1 ml) was added to a solution of [3aR-(3aα,4α,6α,6aα)]-6-[[5-amino-6-Chloro-2-[(3,3,3-trifluoropropyl)thio]-4-pyrimidinyl]-amino]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol (prepared as described in International Patent Application WO 9703084) (8.1 g) in acetonitrile (1000 ml) and the solution heated at 70° C. for 1 hour. The cooled reaction mixture was concentrated and purified (SiO_2, dichloromethane:ethyl acetate 4:1 as eluant) to afford an intermediate which was converted to the subtitle compound by the method of example 1, step e) using the product of step d).

MS (APCI) 587 ($M+H^+$, 100%)

f) [1R-[1α,2α,3β(1R*,2S*),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol

Prepared according to the method of example 1, step h) using the product of step e).

MS (APCI) 547 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 9.43 (1H, d), 7.35–7.28 (2H, m), 7.14–7.02 (1H, m), 5.01–4.96 (2H, m), 4.72–4.69 (2H, m), 4.42 (1H, q), 3.87–3.84 (1H, m), 3.50–3.44 (2H, m), 3.25–3.12 (3H, m), 2.58–2.50 (2H, m), 2.28–2.21 (3H, m), 1.85–1.80 (1H, m), 1.52–1.50 (1H, m), 1.39–1.37 (1H, m).

Example 3

[1S-(1α,2α,3β(1S*,2R*),5β)]-3-[7-[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol,

a) (1R-cis)-Bis(1,1-dimethylethyl)-4-hydroxy-2-cyclopentenylimidodicarbonate

To a suspension of ether washed sodium hydride (60% dispersion in oil; 0.31 g) in tetrahydrofuran (30 ml) was added imidodicarbonic acid bis-(1,1-dimethylethyl)ester (1.84 g). The mixture was stirred at 40° C. for 1 hour. To the mixture, at ambient temperature, was then added (1S-cis)-4-acetoxy-2-cyclopenten-1-ol (0.5 g) and tetrakis (triphenylphosphine)palladium(0) (0.18 g). The reaction mixture was stirred for 24 hours then purified (SiO_2, ethyl acetate: hexane 1:9 as eluant) to give the subtitle compound as a colourless solid (0.90 g).

NMR δH (d_6-DMSO) 1.43 (18H, s), 1.61 (1H, ddd, J=12.3, 7.7, 6.4 Hz), 2.54 (1H, dt, J=12.6, 7.4 Hz), 4.51–4.57 (1H, m), 4.86 (1H, tq, J=8.0, 1.8 Hz), 4.91 (1H, d, J=5.4 Hz), 5.71–5.77 (2H, m).

b) [1R-(1α,2β,3β,4α)]-2,3,4-Trihydroxy-cyclopentenylimidodicarbonic acid, bis(1,1-dimethylethyl) ester

To a solution of the product of step a) (17.1 g) in tetrahydrofuran (500 ml)/water (50 ml) was added N-methylmorpholine-N-oxide (9.4 g) followed by osmium tetroxide (10 ml, 2.5% solution in t-butanol). The mixture was stirred at room temperature for 4 days then treated with sodium hydrosulphite (6.0 g). The suspension was filtered through celite and the product purified (SiO_2, ethyl acetate: hexane 1:1 as eluant) to afford the subtitle compound (19.1 g).

NMR δH (d_6-DMSO) 1.44 (18H, s), 1.46–1.60 (1H, m), 1.97–2.05 (1H, m), 3.55–3.58 (1H, m), 3.66–3.73 (1H, m), 4.11–4.21 (2H, m), 4.54 (1H, d, J=4.8 Hz), 4.56 (1H, d, J=5.9 Hz), 4.82 (1H, d, J=4.6 Hz)

c) [3aR-(3aα,4α,6α,6aα)]-6-Amino-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol, hydrochloride

The product from step b) (17.4 g) in 6M HCl (100 ml)/methanol (500 ml) was stirred for 18 hours. The mixture was evaporated and then azeotroped with toluene (4×200 ml) to give a colourless powder (8.7 g). This solid was suspended in acetone (250 ml) containing 2,2-dimethoxypropane (25 ml) and cHCl (0.2 ml) then heated under reflux for 2 hours. The mixture was cooled, evaporated and azeotroped with toluene (3×200 ml). The residue was dissolved in 20% aqueous acetic acid and stirred for 2 hours. The mixture was evaporated and azeotroped with toluene (4×200 ml) to afford the subtitle compound (10.1 g).

MS (APCI) 174 ($M+H^+$, 100%)

d) [3aR-(3aα,4α,6α,6aα)]-6-[[6-Chloro5-nitro2-(propylthio)-pyrimidin-4yl]amino]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol

A solution of the product from step c) (10.0 g) and N,N-diisopropylethylamine (35 ml) in tetrahydrofuran (600 ml) was stirred for 1 hour. The mixture was filtered and the solution was added over 1 hour to a solution of 4,6-dichloro-5-nitro-2-(propylthio)-pyrimidine (prepared as described in International Patent Application WO 9703084) (25.6 g) in tetrahydrofuran (1000 ml) and stirred for a further 2 hours. The solvent volume was reduced in vacuo and ethyl acetate was added (1000 ml). The mixture was washed with water and the organic layers were dried. evaporated and purified (SiO_2, isohexane-ethyl acetate as eluant) to afford the subtitle compound (14.2 g).

MS (APCI) 405 ($M+H^+$, 100%)

e) [3aR-(3aα,4α,6α,6aα)]-6-[[5-Amino-6-Chloro-2-(propylthio)-pyrimidin-4-yl]amino]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol

Iron powder (3.0 g) was added to a stirred solution of the product of step d) (2.7 g) in acetic acid (100 ml). The reaction mixture was stirred at room temperature for 2 hours, concentrated to half volume, diluted with ethyl acetate and washed with water. The organic phase was dried and concentrated to afford the subtitle compound (2.0 g).

MS (APCI) 375 ($M+H^+$, 100%)

f) [3aR-(3aα,4α,6α,6aα)]-6-[7-Chloro-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol

Isoamyl nitrite (1.1 ml) was added to a solution of the product of step e) (2.0 g) in acetonitrile (100 ml) and the solution heated at 70° C. for 1 hour. The cooled reaction mixture was concentrated and purified (SiO_2, ethyl acetate:isohexane 1:3 as eluant) to afford the subtitle compound (1.9 g).

MS (APCI) 386 ($M+H^+$, 100%)

g) [3aR-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol

The product of step f) (13.2 g) in tetrahydrofuran (200 ml) containing 0.88 ammonia (5 ml) was stirred for 2 hours then concentrated to dryness and the residue partitioned between water and ethyl acetate. The organics were dried and then concentrated to afford the subtitle compound (12.5 g).

MS (APCI) 367 ($M+H^+$, 100%).

h) [3aR-(3aα,4α,6α,6aα)]-[[6-[7-Amino-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol]oxy]acetic acid, methyl ester

To a solution of the product of step g) (0.50 g) in tetrahydrofuran (25 ml) at 0° C., was added butyllithium (0.62 ml of 2.5N in hexanes). After 20 minutes, the suspension was treated with a solution of trifluoromethanesulfonyloxy-acetic acid methyl ester (0.34 g) (prepared according to the method of Biton, Tetrahedron, 1995, 51, 10513) in tetrahydrofuran (10 ml). The resulting solution was allowed to warm to room temperature then concentrated and purified (SiO_2, ethyl acetate: hexane 4:6 as eluant) to afford the subtitle compound (0.25 g).

MS (APCI) 439 ($M+H^+$, 100%).

i) [3aR-(3aα,4α,6α,6aα)]-[[6-[7-Bromo-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol]oxy]acetic acid, methyl ester

The product from step h) (1.1 g) and isoamylnitrite (2.4 ml) in bromoform (30 ml) was heated at 80° C. for 30 minutes. The cooled reaction mixture was purified (SiO_2, ethyl acetate:isohexane 1:4 as eluant) to afford the subtitle compound (0.44 g).

MS (APCI) 502/4 (M+H+), 504 (100%).

j) [3aR-[3aα,4α,6α(1R*,2S*),6aα]]-[[6-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]oxy]acetic acid, methyl ester

To a mixture of the products from step i) (0.80 g) and Example 2, step d) (0.61 g) in dichloromethane (25 ml) was added N,N-diisopropylethylamine (0.85 ml). The resulting solution was stirred at room temperature for 16 hours then concentrated in vacuo. Purification (SiO_2, isohexane:ethylacetate 3:1 as eluant) gave the subtitle compound as a colourless foam (0.77 g).

MS (APCI) 591 ($M+H^+$, 100%)

k)[3aR-[3aα,4α,6α(1R*,2S*),6aα]]-2-[6-[[7-[2-(3,4-Difluorophenyl)cyclopropyl]amino-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol

DIBAL-H® (1.0M solution in hexanes, 5.15 ml) was added to an ice-cooled solution of the product of step j) (0.76 g) in tetrahydrofuran (1 ml) and the solution stirred at this temperature for 2 hours. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (75 ml). A saturated aqueous solution of sodium potassium tartrate (75 ml) was added and the mixture stirred vigorously for 16 hours. The organics were collected and the aqueous re-extracted with ethyl acetate (2x50 ml). The combined organics were dried and concentrated and the residue purified (SiO_2, isohexane:ethylacetate 1:1 as eluant) to give the subtitle compound (0.63 g).

MS (APCI) 563 ($M+H^+$, 100%)

l)[1S-[1α,2α,3β(1S*,2R*),5β]]-3-[7-(2-(3,4-Difluorophenyl)cyclopropylamino)5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol

Prepared according to the method of example 1, step h) using the product of step k).

MS (APCI) 523 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 8.95 (1H, d, J=3.3 Hz), 7.39–7.21 (2H, m), 7.10–7.00 (1H,m),5.12 (1H, d, J=6.4 Hz), 5.05 (1H, d, J=3.6 Hz), 4.96 (1H, q, J=9.0 Hz), 4.62–4.54 (2H,m),3.95 (1H, br s), 3.79–3.73 (1H, m), 3.55–3.47 (4H, m), 3.20–3.13 (1H, m), 2.98–2.81 (2H,m), 2.63 (1H, dt, J=13.6, 8.5 Hz), 2.29–2.21 and 2.16–2.09 (1H, m), 2.07–2.00 (1H,m), 1.73–1.33 (4H, m), 0.99 (3H, t, J=7.4 Hz).

Example 4

[1R-[1α,2α,3β(1R*,2S*),5β]]-3-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol

a) [3aR-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol

Prepared according to the method of Example 3, step g) using [3aR-(3aα,4α,6α,6aα)]-6-[7chloro-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol (prepared as described in International Patent Application WO 9703084). The crude product was purified (SiO_2, methanol:dichloromethane 1:19 as eluant) to give the subtitle compound.

MS (APCI) 381 ($M+H^+$, 100%).

b) [3aR-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylsulfonyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol

Prepared according to the method of example 1, step f) using the product of step a).

MS (APCI) 413 ($M+H^+$, 100%).

c) [3aR-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(butylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol

1-Butanethiol (2.38 ml) in DMF (25 ml) was added to a suspension of sodium hydride (60%, 1.09 g) in DMF (50 ml). After 1 hour a solution of the product of step b) (3.66 g) in DMF (65 ml) was added dropwise and the resulting mixture was stirred overnight. The reaction mixture was added slowly to saturated aqueous sodium bicarbonate (1000 ml) and then extracted into ethyl acetate (3x200 ml). The organic phase was dried ($MgSO_4$) and concentrated in vacuo and the residue purified (SiO_2, methanol:dichloromethane 1:19 as eluant) to give the subtitle compound (3.32 g).

MS (APCI) 395 ($M+H^+$, 100%).

d) [3aR-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(butylthio)-3H-1,2,3-triazolo[4,5d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol, acetate

To a solution of the product from step c) (3.3 g) in dichloromethane (50 ml), was added pyridine (2.7 ml), 4-dimethylaminopyridine (0.4 g) and acetic anhydride (2.0 ml). The mixture was stirred at room temperature overnight, concentrated in-vacuo and purified (SiO_2, diethyl ether:isohexane 3:2 as eluent) to give the subtitle compound (2.7 g).

MS (APCI) 437 ($M+H^+$, 100%).

e) [3aR-(3aα,4α,6α,6aα)]-6-[7-Bromo-5-(butylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol, acetate

Prepared according to the method of example 3, step i) using the product of step d).

MS (APCI) 500/502 ($M+H^+$), 500 (100%).

f) [3aR-[3aα,4α,6α(1R*,2S*),6aα]]-6-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol, acetate

Prepared according to the method of example 3, step j) using the product of example 2, step d) and the product of step e).

MS (APCI) 589 ($M+H^+$, 100%).

g) [1R-[1α,2α,3β(1R*,2S*),5β]]-3-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol

The product of step f) (0.64 g) in 80% aqueous acetic acid (30 ml) was heated at 80° C. for 1 hour. The cooled mixture was poured into saturated sodium bicarbonate solution and extracted into ethyl acetate. The organic phase was dried and concentrated in vacuo to give a gum which was dissolved in methanol (50 ml)/10% aqueous potassium carbonate solution (3 ml). The solution was stirred for 30 minutes, neutralised with acetic acid, and concentrated in vacuo. Purification (SiO_2, methanol:dichloromethane 1:19 as eluent) gave a solid which was recrystallised (acetonitrile) to give the title compound (0.25 g).

MS (APCI) 507 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 9.34 (1H, br), 7.40–7.23 (2H, m), 7.11–7.00 (1H, m), 5.06–4.93 (2H, m), 4.76–4.67 (2H, m), 4.48–4.38 (1H, m), 3.91–3.84 (1H, m), 3.56–3.39 (2H, m), 3.21–3.08 (1H, m), 3.03–2.83 (2H, m), 2.32–2.17 (1H, m), 2.17–2.03 (2H, m), 1.91–1.77 (1H, m), 1.71–1.32 (4H, m), 1.32–1.17 (2H, m), 0.81 (3H, t).

Example 5

[1S-[1α,2β,3β,4α(1S*,2R*)]]-4-[5-(Butylthio)7-[[2-(4-fluorophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-cyclopentane-1,2,3-triol

a) [3aR-[3aα,4α,6α,6aα(1S*,2R*)]]-6-[7-[[(4-Fluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol

Prepared according to the method of example 1, step e) using the product of example 1, step d) and the product of example 3 step f).

MS (APCI) 501 ($M+H^+$, 100%).

b) [3aR-[3aα,4α,6α,6aα(1S*,2R*)]]-6-[[7-[(4-Fluorophenyl)cyclopropyl]amino]-5-(propylsulphonyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol

Prepared according to the method of example 1, step f) using the product of step a).

MS (APCI) 532 ($M+H^+$, 100%).

c) [3aR-[3aα,4α,6α,6aα(1S*,2R*)]]-6-[7-[[(4-Fluorophenyl)cyclopropyl]amino]-5-(butylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol

Prepared according to the method of example 4 step c) using the product of step b).

MS (APCI) 515 ($M+H^+$, 100%).

[1S-[1α,2β,3β,4α(1S*,2R*)]]-4-[S-(Butylthio)-7-[[2-(4-fluorophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-cyclopentane-1,2,3-triol

Prepared according to the method of example 1 step h) using the product of step c).

MS (APCI) 575 ($M+H^+$, 100%).

NMR δH (d_6-DMSO) 7.26–7.22 (2H, m), 7.11 (2H, t), 4.99–4.90 (1H, m), 4.67–4.63 (1H, m), 3.93 (1H, s), 3.77 (1H, bs), 3.35–3.13 (1H, m), 3.00–2.80 (2H, m), 2.59–2.51 (1H, m), 2.15–2.11 (1H, m), 1.91–1.86 (1H, m), 1.53–1.41 (3H, m), 1.35–1.30 (1H, m), 1.22 (2H, sex), 0.80 (3H, t).

Example 6

[1S-[1α,2α,3β(1S*,2R*),5β)]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol

a) [1S-(1α,2α,3β(1S*,2R*),5β)]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylsulphonyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol

The subtitle compound was prepared according to the method of Example 1, step f) using the product of Example 3, step 1.

MS(APCI) 555($M+H^+$, 100%)

b) [1S-(1α,2α,3β(1S*,2R*),5β)]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl[amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol

The title compound was prepared according to the method of Example 1, step g) using the product of step a).

MS(APCI) 555 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 9.45 (1H, d), 7.36–7.05 (3H, m), 5.05 (1H, d), 5.02 (1H, d), 4.95 (1H, m), 4.60 (2H, m), 3.95 (1H, m), 3.86 (1H, m), 3.47 (4H, m), 3.30–3.11 (3H, m), 2.63–2.49 (3H, m), 2.19 (1H, m), 2.00 (1H, m), 1.53 (1H, m), 1.40 (1H, m).

Example 7

[1S-[1α,2α,3β,5β(1S*,2R*)]]-3-(2Hydroxyethoxy)-5-[7-(2-phenylcyclopropyl)amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-cyclopentane-1,2-diol

a) (1S-cis)-2-[[4-[[6-Chloro-5-nitro-2-[(3,3,3-trifluoropropyl)thio]-4-pyrimidinyl]amino]-2-cyclopenten-1-yl]oxy]-acetic acid, ethyl ester

A solution of sodium azide (4.70 g) in degassed water (25 ml) was added to a solution of (1R,4S)-4-hydroxy-2-cyclopenten-1-yl acetate (9.99 g) in tetrahydrofuran (60 ml) and stirred for 10 min. Tetrakis(triphenylphosphine) palladium(0) (365 mg) was added and stirred for 10 min. The aqueous layer was separated and extracted twice with ethyl acetate. The combined organic layers were dried ($MgSO_4$), concentrated and purified on a short column (SiO_2, ethyl acetate:isohexane 1:2 as eluant) to afford a yellow oil. This was dissolved in tetrahydrofuran (25 ml) and slowly added to a suspension of sodium hydride (2.94 g, 60% dispersion in oil) in tetrahydrofuran (60 ml) at −78° C. A solution of ethyl bromoacetate (8.2 ml) in tetrahydrofuran (5 ml) was added and the mixture was allowed to warm to 20° C. and stirred for 30 min. Aqueous ammonium chloride solution was added and the mixture was extracted with ether. The organic layers were dried ($MgSO_4$), concentrated and purified (SiO_2, ether:isohexane 1:5 as eluant) to afford a colourless oil. A solution of this oil and triphenylphosphine (17.89 g) in tetrahydrofuran (90 ml) was

stirred for 10 min. Water (15 ml) was added and the solution was stirred for 18 hours. The solvent was removed in vacuo and the residue azeotroped with toluene then purified (SiO_2, ethyl acetate then ethyl acetate-methanol-ammonia (90:9:1) as eluant) to afford a pale yellow oil (7.14 g).

A solution of this compound in tetrahydrofuran (50 ml) was added over 25 min to a solution of 4,6-dichloro-5-nitro-2-[(3,3,3-trifluoropropyl)thio]pyrimidine (prepared as described in International Patent Application WO 9703084) (24.8 g) and N,N-diisopropylethylamine (77.5 ml) in dry tetrahydrofuran (100 ml) and then stirred for 30 minutes. Water was added and the mixture was extracted with ether (three times). The organic layers were dried ($MgSO_4$), concentrated and purified (SiO_2, ethyl acetate:isohexane 1:4 as eluant) to afford the subtitle compound (7.39 g).

MS (APCI) 36719 (M-(EtO_2CCH_2O)$^+$), 367 (100%)

b) (1S-cis)2-[[4-[7-Chloro-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-2-cyclopenten-1-yl]oxy]-acetic acid, ethyl ester

Prepared according to the method of example 3, steps e) and f) using the product of step a).

MS (APCI) 348/50 (M-(EtO_2CCH_2O)$^+$), 348 (100%).

c) [1S-(cis)]2-[[4-[7-Amino-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3triazolo[4,5-d]pyrimidin-3-yl]-2-cyclopenten-1-yl]oxy]-acetic acid, ethyl ester

Prepared according to the method of example 3, step g) using the product of step b).

MS (APCI) 433 (M+H$^+$, 100%).

d) [1S-(cis)]2-[[4-[7-Amino-5-[(3,3,3-trifluoropropyl)thiol-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-2-cyclopenten-1-yl]oxy]-1-ethanol

Prepared according to the method of example 3, step k) using the product of step c).

MS (APCI) 391 (M+H$^+$, 100%).

e) [3aR-(3aα,4α,6α,6aα)]-2-[6-[7-Amino-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yloxy]ethanol

A solution of the product from step d) (454 mg), osmium tetroxide (0.17 ml of 0.1M solution in t-butanol), N-methylmorpholine N-oxide (210 mg) and pyridine (0.09 ml) in acetone (5 ml) and water (1 ml) was heated at 70° C. for 5 hours. Sodium hydrosulfite (330 mg) in water (1 ml) was added, the solvent was remove in vacuo and the residue azeotroped with toluene. A solution of this and p-toluenesulfonic acid (50 mg) in acetone (5 ml) and 2,2-dimethoxypropane (2 ml) was stirred for 3 h. The solvent was remove in vacuo, aq sodium hydrogen carbonate solution added and the mixture was extracted with ethyl acetate. The organic layers were dried ($MgSO_4$), concentrated and purified (SiO_2,isohexane:acetone 5:2 as eluant) to afford the subtitle compound as a white solid (367 mg).

MS (APCI) 465 (M+H$^+$, 100%)

f) [3aR-[3aα,4α,6α,6aα)]-2-[6-[7-Bromo-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5 d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yloxy]ethanol

Prepared according to the method of Example 3, step i) using the product of step e).

MS (APCI) 528130 (M+H$^+$), 528 (100%)

g) [3-[3aα,4α,6α(1R*,2S*),6aα]-2-[6-(7-Phenylcyclopropyl)amino]-5-[(3,3,3-trifluoropropyl) thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-1,3-dioxol-4-yloxy]ethanol

Prepared according to the method of Example 3, step j) using the product of step f) and (1R-trans)-2-phenyl-cyclopropanamine, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L. A. Mitscher et al., J. Med. Chem. 1986, 29, 2044).

MS (APCI) 581 (M+H$^+$, 100%)

h) [1S-[1α,2α,3β,5β(1S*,2R*)]]-3-(2Hydroxyethoxy)-5-[7-(2-phenylcyclopropyl)amino]-5-[(3,3,3-trifluoropropyl) thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-cyclopentane-1,2-diol

Prepared according to the method of Example 1, step h) using the product of step g).

MS (APCI) 540 (M+H$^+$, 100%).

NMR δH (d_6-DMSO) 7.35–7.16 (5H, m), 4.97 (1H, q), 4.62–4.54 (1H, m), 3.98–3.92 (1H, m), 3.78–3.72 (1H, m), 3.55–3.44 (4H, m), 3.26–3.19 (2H, m), 3.16–3.07 (1H, m), 2.70–2.61 (1H, m), 2.58–2.52 (1H, m), 2.23–2.18 (1H, m), 2.05–1.97 (1H, m), 1.86 (1H, s), 1.54–1.46 (1H, m), 1.38–1.30 (1H, m).

Example 8

[1S-[1α,2β,3β,4α(1S*, 2R*)]]-4-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2,3-triol

a) [3aR-[3aα,4α,6α(1R*,2S*),6aα]-6-[[7-[(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol

The subtitle compound was prepared according to the method of Example 1, step e) using the product of Example 3, step f) and the product of example 2, step d).

MS (APCI) 519 (M+H$^+$, 100%).

b) [3aR-[3aα,4α,6α(1R*,2S*),6aα]]-6-[[7-[(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylsulfonyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol

The subtitle compound was prepared according to the method of Example 1, step f) using the product of step a).

MS (APCI) 551 (M+H$^+$, 100%).

c) [3aR-[3aα,4α,6α(1R*,2S*),6aα]]-6-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol

The subtitle compound was prepared according to the method of Example 4, step c) using the product of step b).

MS (APCI) 533 (M+H$^+$, 100%)

d) [1S-[1α,2β,3β,4α(1S*, 2R*)]]-4-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2,3-triol

The title compound was prepared according to the method of Example 1, step h) using the product of step c).

NMR δH (d_6-DMSO) 7.15–6.98 (3H, m), 6.67 (1H, s), 5.11–5.09 (1H, m), 4.82–4.76 (1H m), 4.34–4.21 (3H, m), 3.7 (1H, s), 3.2–2.92 (4H, m), 2.77 (1H, m), 2.42–2.36 (1H, m), 2.2–2.18 (1H, m), 1.42–1.25 (6H, m), 0.9 (3H, q).

MS (APCI) 493 (M+H$^+$, 100%)

Example 9

[1S-[1α,2α,3β(1S*,2R2*),5β]]-3-[5-(Butylthio)-7-[(2-phenylcyclopropyl)amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxethoxy)-cyclopentane-1,2-diol

a) [3aS-(3aα,4α,6α,6aα)]-[Tetrahydro-6-hydroxy-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester

Potassium carbonate (39.3 g) was added to a suspension of [3αR-(3aα,4α,6α,6aα)]-6-amino-tetrahydro-2,2-

dimethyl-4H-cyclopenta-1,3-dioxol-4-ol, hydrochloride, (prepared as described in WO 9905142) (27.1 g) in 4-methyl-2-pentanone (500 ml). Water (150 ml) was then added followed by dropwise addition of benzyl chloroformate (23.1 g). The reaction mixture was stirred at room temperature for 4 hours before the organic phase was separated. The aqueous phase was extracted with 4-methyl-2-pentanone (2x50 ml). The combined organics were concentrated and the residue was purified (SiO_2, dichloromethane:methanol, 95:5 to 90:10 as eluant) to give the subtitle compound (39.23 g).

NMR δH ($CDCl_3$) 7.32 (5H, m), 5.65 (1H, br s), 5.10 (2H, br s), 4.59 (1H, d), 4.48 (1H, d), 4.27 (1H, m), 4.19 (1H, br m), 2.24 (1H, br s), 1.69 (1H, d), 1.41 (3H, s), 1.26 (3H, s).

b) [3aS-(3aα,4α,6α,6aα)]-[2,2-Dimethyl-6-(2-hydroxyethoxy)-tetrahydro-4H-cyclopenta-1,3-dioxol-4-yl]-carbamic acid, phenylmethyl ester

Potassium tert-butoxide (3.6 g) in tetrahydrofuran (20 ml) was added over 5 minutes to a solution of the product from step a) (39.23 g) in tetrahydrofuran (200 ml). After 15 minutes, ethyl bromoacetate (3.7 ml) in tetrahydrofuran (10 ml) was added dropwise. The mixture was stirred at 0° C. for 10 minutes, then further ethyl bromoacetate was added (3.7 mlx4).

The reaction mixture was stirred at 0° C. a further 2 hours. Lithium borohydride (2.79 g) was then added portionwise to the resulting suspension and the reaction mixture was stirred at <5° C. for 16 hours. Glacial acetic acid (23 g) was added dropwise to the cold mixture. After stirring for 30 minutes, water (100 ml) was added dropwise and the resulting mixture was stirred for 30 minutes. The phases were then separated and the aqueous phase was extracted with ethyl acetate. The combined organics were washed with saturated sodium bicarbonate and brine, dried and concentrated. The residue was purified (SiO_2, ethyl acetate:hexane, 25:75 to 50:50 as eluant) to give the subtitle compound (38.6 g).

MS (APCI) 218 ($M+H^+$, 100%).

c)) [3aR-(3aα,4α,6α,6aα)]-2-[[6-Amino-2,2-dimethyl-tetrahydro-4H-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol

A slurry of 5% palladium on charcoal (4 g) in ethanol was added to a solution of the product from step b) (39.96 g) in ethanol (250 ml) and the mixture was hydrogenated at 1.2 bar for 20 hours. The catalyst was filtered off and the filtrate was concentrated to give the subtitle compound (23.65 g).

MS (APCI) 160 ($M+H^+$, 100%).

d) 2-(Butylthio)-4,6-dichloropyrimidine-5-amine

The subtitle compound was prepared according to the method of example 3, step e) using 2-(butylthio)-4,6-dichloro-5-nitro-pyrimidine (prepared as described in DE 2223644).

NMR δH ($CDCl_3$) 4.20 (2H, br s), 3.10 (2H, t), 1.70 (2H, m), 1.47 (2H, m), 0.95 (3H, t).

e) (3aR-(3aα,4α,6α,6aα)]-2-[[6-[[S-Amino-2-(butylthio)-6-chloro-pyrimidin-4-yl]amino]-tetrahydro-2,2-dimethyl4H-cyclopenta-1,3-dioxol-4-yl]oxy]ethanol

The subtitle compound was prepared according to the method of example 3, step d) using the products of steps c) and d).

MS (APCI) 433 ($M+H^+$, 100%).

f) [3aR-[3aα,4α,6α(1R*,2S*),6aα]]-2-[6-[[5-(Butylthio)-7-chloro-3H-1,2,3-trizolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1 ,3-dioxol-4-yl] oxy]-ethanol

The subtitle compound was prepared according to the method of Example 3, step f) using the product of step e).

NMR δH ($CDCl_3$) 5.53 (1H, m), 5.21 (1H, m), 4.88 (1H, d), 4.05 (1H, m), 3.59 (4H, m), 3.24 (2H, t), 2.70 (1H, m), 2.53 (1H, m), 2.13 (1H, t), 1.79 (2H, m), 1.55 (5H, m), 1.37 (3H, s), 0.98 (3H, t).

g) [3aR-[3aα,4α,6α(1R*,2S*),6aα]-2-[6-[[5-(Butylthio)-7-[2-phenylcyclopropyl]amino-3H-1,2,3-triazolo[4,5-d] pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol

The subtitle compound was prepared according to the method of Example 3, step j) using the product of step f).

MS (APCI) 541 ($M+H^+$, 100%).

h) [1S-[1α,2α,3β(1S*,2R*),5β]]-3-[5-(Butylthio)-7-[(2-phenylcyclopropyl)amino]-3H-1,2,3-triazolo[4,5-d] pyrimidin-3-yl]-5-(2-hydroxethoxy)-cyclopentane-1,2-diol

The title compound was prepared according to the method of example 1, step h) using the product of step g).

MS (APCI) 501 ($M+H^+$, 100%)

NMR δH (d_6-DMSO) 9.33 (1H, d), 7.30 (2H, m), 7.18 (3H, m), 5.12 (1H, d), 5.04 (1H, d), 4.96 (1H, q), 4.59 (2H, m), 3.94 (1H, s), 3.76 (1H, m), 3.51 (4H, m), 3.22 (1H, m), 2.98 (1H, m), 2.86 (1H, m), 2.65 (1H, m), 2.14 (1H, m), 2.05 (1H, m), 1.21–1.53 (6H, m), 0.80 (3H, t).

Pharmacological Data

The preparation for the assay of the P_{2T} ($P2Y_{ADP}$ or $P2T_{AC}$) receptor agonist/antagonist activity in washed human platelets for the compounds of the invention was carried out as follows.

Human venous blood (100 ml) was divided equally between 3 tubes, each containing 3.2% trisodium citrate (4 ml) as anti-coagulant. The tubes were centrifuged for 15 minutes at 240 G to obtain a platelet-rich plasma (PRP) to which 300 ng/ml prostacyclin was added to stabilize the platelets during the washing procedure. Red cell free PRP was obtained by centrifugation for 10 minutes at 125G followed by further centrifugation for 15 minutes at 640 G. The supernatant was discarded and the platelet pellet resuspended in modified, Calcium Free Tyrode solution (10 ml) (CFT), composition: NaCl 137 mM, $NaHCO_3$ 11.9 mM, NaH_2PO_4 0.4 mM, KCl 2.7 mM, $MgCl_2$ 1.1 mM, dextrose 5.6 mM, gassed with 95% O_2/5% CO_2 and maintained at 37° C. Following addition of a further 300 ng/ml PGI_2, the pooled suspension was centrifuged once more for 15 minutes at 640 G. The supernatant was discarded and the platelets resuspended initially in 10 ml CFT with further CFT added to adjust the final platelet count to $2x10^5$/ml. This final suspension was stored in a 60 ml syringe at 3° C. with air excluded. To allow recovery from PGI_2-inhibition of normal function, platelets were used in aggregation studies no sooner than 2 hours after final resuspension.

In all studies, 3 ml aliquots of platelet suspension were added to tubes containing $CaCl_2$ solution (60 μl of 50 mM solution with a final concentration of 1 mM). Human fibrinogen (Sigma, F 4883) and 8-sulphophenyltheophylline (8-SPT which was used to block any P_1-agonist activity of compounds) were added to give final concentrations of 0.2 mg/ml (60 μl of 10 mg/ml solution of clottable protein in saline) and 300 nM (10 μl of 15 mM solution in 6% glucose), respectively. Platelets or buffer as appropriate were added in a volume of 150 μl to the individual wells of a 96 well plate. All measurements were made in triplicate in platelets from each donor.

The agonist/antagonist potency was assessed as follows.

Aggregation responses in 96 well plates were measured using the change in absorbance given by the plate reader at 660 nm. Either a Bio-Tec Ceres 900C or a Dynatech MRX were used as the plate reader.

The absorbance of each well in the plate was read at 660 nm to establish a baseline figure. Saline or the appropriate

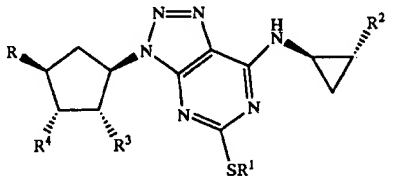
solution of test compound was added to each well in a volume of 10 μl to give a final concentration of 0, 0.01, 0.1, 1, 10 or 100 mM. The plate was then shaken for 5 min on an orbital shaker on setting 10 and the absorbance read at 660 nm. Aggregation at this point was indicative of agonist activity of the test compound. Saline or ADP (30 mM; 10 μl of 450 mM) was then added to each well and the plate shaken for a further 5 min before reading the absorbance again at 660 nm.

Antagonist potency was estimated as a % inhibition of the control ADP response to obtain an IC_{50}. Compounds exemplified have pIC_{50} values of more than 5.0.

What is claimed is:

1. A compound of formula (I)

(I)



wherein:

R^1 is C_{3-5} alkyl optionally substituted by one or more halogen atoms;

R^2 is a phenyl group, optionally substituted by one or more fluorine atoms;

R^3 and R^4 are both hydroxy;

R is XOH, where X is CH_2, OCH_2CH_2 or a bond;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt provided that:

when X is CH_2 or a bond, R^1 is not propyl;

when X is CH_2 and R^1 is $CH_2CH_2CF_3$, butyl or pentyl, the phenyl group at R^2 must be substituted by fluorine;

when X is OCH_2CH_2 and R^1 is propyl, the phenyl group at R^2 must be substituted by fluorine.

2. A compound according to claim 1 in which R^1 is 3,3,3,-trifluoropropyl, butyl or propyl.

3. A compound according to claim 1 in which R^2 is phenyl or 4-fluorophenyl or 3,4-difluorophenyl.

4. A compound according to claim 1 in which R is CH_2OH or OCH_2CH_2OH.

5. A compound according to claim 1 which is:

[1R-[1α,2α,3β(1R*,2S*),5β]]-3-[7-[[2-(4-Fluorophenyl) cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1, 2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol;

[1R-[1α,2α,3β(1R*,2S*),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol;

[1S-(1α,2α,3β(1S*,2R*),5β]]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol;

1R-[1α,2α,3β(1R*,2S*),5β]]-3-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo [4,5-d]pyrimidin-3-yl]-5-(hydroxymethyl)-cyclopentane-1,2-diol;

[1S-[1α,2β,3β,4α(1S*,2R*)]]-4-[5-(Butylthio)-7-[[2-(4-flurophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo[4,5-d] pyrimidin-3-yl]-cyclopentane-1,2,3-triol;

[1S-(1α,2α,3β(1S*,2R*),5β]-3-[7-[[2-(3,4-Difluorophenyl) cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1, 2,3-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol;

[1S-[1α,2α,3β,5β(1S*,2R*)]]-3-(2-Hydroxyethoxy)-5-[7-(2-phenylcyclopropyl)amino]-5-[(3,3,3-trifluoropropyl) thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-cyclopentane-1,2-diol [1S-[1α,2β,3β,4α(1S*,2R*)]]-4-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl] amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl] cyclopentane-1,2,3-triol;

[1S-[1α,2α,3β(1S*,2R*),5β]]-3-[5-(Butylthio)-7-[(2-phenylcyclopropyl)amino]-3H-1,2,3-triazolo[4,5-d] pyrimidin-3-yl]-5-(2-hydroxethoxy)-cyclopentane-1,2-diol;

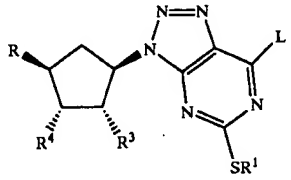
or pharmaceutically acceptable salts or solvates thereof, or solvates of such salts.

6. A pharmaceutical composition comprising a compound according to claim 1 in combination with a pharmaceutically acceptable diluent, adjuvent and/or carrier.

7. A method of treatment of post-myocardial infarction which comprises administering to a patient suffering therefrom a therapeutically effective amount of a compound according to claim 1.

8. A process for the preparation of a compound of formula (I) which comprises reacting a compound of formula (II):

(II)



where R, R^1, R^3 and R^4 are as defined in claim 1, or are protected derivatives thereof, or R^3 and R^4 together form a bond in the 5-membered ring, or R is CH_2CH_2OR' where R' is C_{1-6} alkyl or benzyl, and L is a leaving group, with a compound of formula (III):

(III)

where R^2 is defined in claim 1 or is a protected derivative thereof, in the presence of a base in an inert solvent at ambient or elevated temperature, and optionally thereafter and in any order:

converting one or more functional groups into further functional groups;

removing any protecting groups;

forming a pharmaceutically acceptable salt or solvate, or a solvate of such a salt.

9. The compounds:

[3aR-[3aα,4α,6α(1R*,2S*),6aα]]-6-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-(propylsulphonyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol;

[[3aR-[3aα,4α,6α(1R*,2S*),6aα]]-6-[7-[[2-(4-Fluorophenyl)cyclopropyl]amino]-5-[(3,3,3-trifluoropropyl)lthio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol;

[3aR-[3aα,4α,6α(1R*,2S*),6aα]-6-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-[(3,3,3-

trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol;

[3aR-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol;

[3aR-(3aα,4α,6α,6aα)]-[[6-[7-Amino-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol]oxy]acetic acid, methyl ester;

[3aR-(3aα,4α,6α,6aα)]-[[6-[7-Bromo-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol]oxy]acetic acid, methyl ester.

10. The compounds:

[3aR-[3aα,4α,6α(1R*,2S*),6aα]]-[[6-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]oxy]acetic acid, methyl ester;

[3aR-[3aα,4α,6α(1R*,2S*),6aα]]-6-[[7-[2-(3,4-Difluorophenyl)cyclopropyl]amino-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol;

[3aR-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol;

[3aR-(3aα,4α,6aα)]-6-[7-Amino-5-(propylsulfonyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol;

11. The compounds:

[3aR-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(butylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol;

[3aR-(3aα,4α,6α,6aα)]-6-[7-Amino-5-(butylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol, acetate;

[3aR-(3aα,4α,6α,6aα)]-6-[7-Bromo-5-(butylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol, acetate;

[3aR-[3aα,4α,6α(1R*,2S*),6aα]]-6-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-methanol, acetate;

[3aR-[3aα,4α,6α,6aα(1S*,2R*)]]-6-[7-[[(4-Fluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimdin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol;

[3aR-[3aα,4α,6α,6aα(1S*,2R*)]]-6-[[7-[(4-Fluorophenyl)cyclopropyl]amino]-5-(propylsulphonyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol;

12. The compounds:

[3aR-[3aα,4α,6α,6aα(1S*,2R*)]]-6-[7-[[(4-Fluorophenyl)cyclopropyl]amino]-5-(butylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol;

[1S-(1α,2α,3β(1S*,2R*),5β)]-3-[7-[[2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylsulphonyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol;

(1S-cis) 2-[[4-[7-Chloro-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-2-cyclopenten-1-yl]oxy]-acetic acid, ethyl ester;

[1S-(cis)] 2-[[4-[7-Amino-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-2-cyclopenten-1-yl]oxy]-acetic acid, ethyl ester;

[1S-(cis)] 2-[[4-[7-Amino-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-2-cyclopenten-1-yl]oxy]-1-ethanol;

13. The compounds:

[3aR-(3aα,4α,6α,6aα)]-2-[6-[7-Amino-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yloxy]ethanol;

[3aR-(3aα,4α,6α,6aα)]-2-[6-[7-Bromo-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yloxy]ethanol;

[3aR-[3aα,4α,6α(1R*,2S*),6aα]-2-[6-(7-Phenylcyclopropyl)amino]-5-[(3,3,3-trifluoropropyl)thio]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-1,3-dioxol-4-yloxy]ethanol;

[3aR-[3aα,4α,6α(1R*,2S*),6aα]-6-[[7-[(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol;

[3aR-[3aα,4α,6α(1R*,2S*),6aα]]-6-[[7-[(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylsulfonyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol;

[3aR-[3aα,4α,6α(1R*,2S*),6aα]]-6-[5-(Butylthio)-7-[[2-(3,4-difluorophenyl)cyclopropyl]amino]-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-ol;

[3aR-[3aα,4α,6α(1R*,2S*),6aα]]-2-[6-[[5-(Butylthio)-7-chloro-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol;

[3aR-[3aα,4α,6aα(1R*,2S*),6aα]]-2-[6-[[5-(Butylthio)-7-[2-phenylcyclopropyl]amino-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]oxy]-ethanol;

14. A method of treatment of stroke which comprises administering to a person suffering therefrom a therapeutically effective amount of the compound according to claim 1.

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MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,525,060	**$2,480.00**	**$0.00**	**07/02/10**	**09/508,195**	**02/25/03**	**03/08/00**	**08**	**NO**	**3831401**